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碩士論文

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Master’s Thesis

台灣人類免疫缺乏病毒帶原者與男性性腺功能低下症之盛行率與相關因子研究

Hypogonadism among HIV-positive men who have sex with men in Taiwan: prevalence and associated factors

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口試委員會審定書
MASTER'S THESIS ACCEPTANCE CERTIFICATE
NATIONAL TAIWAN UNIVERSITY

台灣人類免疫缺乏病毒帶原者與男性性腺功能低下症之盛行率與相關因子研究

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本論文係林冠宇 P11421304 在國立臺灣大學臨床醫學研究所完成之碩士學位論文，於民國 113 年 7 月 5 日承下列考試委員審查通過及口試及格，特此證明。

The undersigned, appointed by the Graduate Institute of Clinical Medicine on 5th July 2024 have examined a Master's Thesis entitled above presented by Kuan-Yu, Lin P11421304 candidate and hereby certify that it is worthy of acceptance.

口試委員 Oral examination committee:

施翔蓉 洪健清 楊孝勳

（指導教授 Advisor）

系（所、學位學程）主管 Director: 周祖述

誌謝

時間回到研修醫師第一年，因為內分泌關於「年齡相關之睪固酮低下是否需要治療」的辯論主題，讓我對於男性性腺激素感到興趣。又在教科書上讀到關於人類免疫缺乏病毒帶原者是男性性腺功能低下症的風險之一，因而啟發了研究台灣本土族群的盛行率和危險因子研究。非常感謝指導老師施翔蓉教授在初聽到學生這個構想時，非常支持及鼓勵，並帶領學生拜訪這領域的感染科權威洪健清教授。本研究收案族群皆是從感染科門診而來，因此非常感激洪教授從研究構想到計畫執行的指導，並且協調感染科主治醫師和個管師團隊進行病人實際收案，前後將近一年的時間。感謝台大醫院的師長們劉旺達主治醫師、孫幸筠主治醫師、莊祐中主治醫師，以及在雲林分院期間林綺英、蔡明叡主治醫師無條件熱心協助門診病人的收案，以及針對過程中遇到的困難給予建議。同時也感謝勞苦功高的感染科個管師團隊劉玟君、張喜雁、陳伶雅、羅玉珍、巫沛瑩、陳怡婷、李貴祺以及雲林分院個管師美玲、怡君不斷的協助聯絡病患、填寫問卷和抽血，以及施翔蓉教授的助理莊盈盈、朱怡協助檢體的處理和相關資料的建檔、沒有你們的幫忙這份研究是無法完成的。

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中文摘要

背景簡介：

男性性腺功能低下在 HIV 感染的族群相當常見，早期的流行病學研究盛行率高達 29%至 50%，先前國外流行病學調查顯示 HIV 男性族群性腺功能低下的盛行率大約在 9%至 16%之間。研究關於 HIV 感染的族群和男性性腺功能低下的可能相關因子包括體重下降程度、CD4 數量、體脂肪等等。成年男性睪固酮不足的臨床表現包括性慾下降、勃起功能障礙、骨質密度降低、肌肉質量下降、憂鬱以及代謝症候群等等，而研究發現 HIV 陽性族群，血中低睪固酮濃度和體重下降、肌肉流失、運動表現及衰老指數呈現相關性。根據 2018 年美國內分泌學會治療指引，針對 HIV 陽性族群的男性性腺功能低下症合併體重減輕，建議短期睪固酮補充以維持體重和增加瘦體質量。在此研究之前，文獻尚無關於亞洲族群 HIV 帶原男性其性腺功能低下症的盛行率、危險因子及臨床表現之探討。

目的：

研究台灣 HIV 帶原者其男性性腺功能低下症的盛行率，和未感染 HIV 的一般族群比較，並進一步分析可能的危險因子。

方法：

在這單一中心、橫斷性研究中，自 2021 年 2 月至 2022 年 11 月這段期間，慢性 HIV 帶原、穩定服用抗病毒藥物且測不到病毒量的 20 歲以上男同志（men who have sex with men，下稱 MSM）受試者透過臺大醫院和臺大雲林分院感染科門診加入試驗。未感染 HIV 的 MSM 對照組來自匿名篩檢計畫和政府補助之公費暴露前預防藥物（PrEP）門診。相關臨床資料包括年齡、身體質量指數、慢性病等透過問卷和電子病歷加以記錄。受試者填寫美國聖路易大學老化男人睪固酮低下問卷

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（ADAM，Androgen Deficiency in Aging Male），以評估是否有睪固酮低下之症狀。受試者於早上空腹抽血檢驗血清總睪固酮、白蛋白、性荷爾蒙結合球蛋白以計算游離睪固酮之濃度，同時測量可能影響性腺功能的生化指數和賀爾蒙。生化意義的性腺功能低下（biochemical hypogonadism）定義為血清游離睪固酮濃度小於 63.5 pg/mL。有症狀之性腺功能低下（symptomatic hypogonadism）定義為低血清游離睪固酮濃度合併 ADAM 問卷篩檢結果陽性。本研究使用多元線性回歸分析和血清游離睪固酮濃度相關的臨床因子。此外，在相同年齡分層下，我們比較 HIV 帶原者和未感染 HIV 之對照組在性腺功能低下症的盛行率有無差異。

結果：

本研究一共納入 447 位 HIV 帶原者和 124 位 HIV 陰性的 MSM 受試者。HIV 帶原組的年齡顯著大於對照組（中位數 41 歲 versus 29.5 歲），慢性病的盛行率也較高。HIV 帶原組診斷中位數 8.5 年，CD4 數量中位數 482 顆/微升。分別有 11.6%的帶原組和 1.6%的對照組呈現生化意義的性腺功能低下，而分別有 8.3%的帶原組和 1.6%的對照組呈現有症狀之性腺功能低下。在 HIV 帶原組當中，最常見次發性性腺功能低下，佔 8.9%。而亞臨床和原發性性腺功能低下分別佔 5.4%和 2.7%。在小於三十五歲的年輕次分群，HIV 帶原的有無對於血清游離睪固酮濃度和性腺功能低下的盛行率無顯著差別。多元線性回歸分析顯示血清游離睪固酮濃度隨著年齡和身體質量指數的上升而顯著下降，而和 HIV 帶原狀態、甲狀腺功能、泌乳激素濃度以及其他共病症無顯著關聯性。進一步分析 HIV 帶原組別，血清游離睪固酮濃度和 HIV 感染時間呈現負相關，而和核類反轉錄抑制劑（NRTI）呈現正相關。

討論：

這項研究是迄今針對華人 MSM 族群性腺功能低下症的最大規模之橫斷性研

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究。有症狀之性腺功能低下在研究中 HIV 帶原族群的盛行率為 8.3%，略低於國外的研究族群。究其原因，原發性之性腺功能低下的比例和義大利的研究差不多，而次發性性腺功能低下的比例則低於文獻，因此我們推測 HIV 帶原族群整體健康狀況的改善、病毒量的抑制以及收案時排除干擾睪固酮測量的藥物等，應是本研究盛行率較低的原因。研究中大部分 HIV 帶原者（96.6%）皆使用 NRTI，未使用的五名受試者其藥物組合 dolutegravir 和 rilpivirine 文獻中並未發現和睪固酮濃度相關，因此 NRTI 和睪固酮濃度的相關性仍有待進一步研究確認。最後，本研究的限制包括帶原組和對照組之年齡差距較大、使用單次睪固酮檢測作為診斷標準、以及排除正在使用睪固酮製劑的受試者，可能造成評估真正性腺功能低下盛行率的誤差。

結論：

本研究發現台灣 HIV 帶原者其男性性腺功能低下症的盛行率較國外研究略低，但高於研究中未感染 HIV 的族群。HIV 帶原和未感染 HIV 兩組之間性腺功能低下症之盛行率差異主要來自於年齡的差距。進一步分析發現血清游離睪固酮的濃度和年齡及身體質量指數呈現負相關，而和 HIV 感染與否沒有顯著相關。

中文關鍵字：年齡;身體質量指數;人類免疫缺乏病毒;性腺功能低下;睪固酮

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英文摘要

Background:

Hypogonadism is common among people with HIV (PWH), with prevalence around 9% to 16% in different studies. Risk factors associated with hypogonadism in PWH included weight loss, CD4 counts, body fat. Studies regarding androgen deficiency in PWH reported loss of lean body and muscle mass, deterioration in exercise functional capacity, frailty, and poor health status. Existing data regarding prevalence, clinical manifestations and risk factors associated with male hypogonadism are limited in PWH in Asian populations.

Objective:

We aimed to investigate the clinical manifestations and prevalence of hypogonadism among PWH in Taiwan and compare them with individuals without HIV infection. We further explored the factors associated with serum free testosterone levels in PWH.

Methods:

This cross-sectional study enrolled adult men who have sex with men (MSM) on stable antiretroviral therapy with suppressed plasma HIV-1 RNA levels from February 2021 to November 2022 at National Taiwan University Hospital (NTUH) and NTUH Yunlin Branch. MSM without HIV, including those seeking anonymous HIV testing, and participants in pre-exposure prophylaxis (PrEP) program, were enrolled as the comparison group. Clinical data, including demographics and comorbidities, were collected through questionnaires and electronic medical records. Androgen Deficiency in Aging Men (ADAM) questionnaire was performed to evaluate symptoms of hypogonadism in the participants. Morning fasting levels of serum free testosterone, sex hormone-binding globulin, and other related hormones were obtained. Biochemical hypogonadism was defined by serum free testosterone level < 63.5 pg/mL. Symptomatic

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hypogonadism was defined by low free testosterone plus positive ADAM questionnaire result. Multiple linear regression analysis was conducted to evaluate the relationship between serum free testosterone levels and the collected clinical variables. Furthermore, MSM without HIV infection were enrolled and compared with HIV-positive group within the same age stratification.

Results:

In our study, 447 MSM with HIV and 124 MSM without HIV were included. Compared to MSM without HIV, those with HIV were older (median age 41 versus 29.5 years) and had a higher prevalence of comorbidities such as HBsAg and anti-HCV positivity, hypertension, diabetes, and hyperlipidemia. In MSM with HIV, the median HIV infection duration was 8.5 years, with a median CD4 count of 482 cells/μL. Biochemical hypogonadism was more prevalent in MSM with HIV (11.6%) than in those without (1.6%). Symptomatic hypogonadism also showed higher prevalence in MSM with HIV (8.3% vs. 1.6%). Secondary hypogonadism was the most common in MSM with HIV (8.9%), followed by subclinical (5.4%) and primary hypogonadism (2.7%). Among MSM aged <35 years, there were no significant differences in serum free testosterone levels or prevalences of hypogonadism between the two groups. Multiple linear regression analysis revealed that serum free testosterone levels significantly decreased with increasing age (a decrease of 1.14 pg/mL per 1-year increase) and higher body-mass index (BMI) (a decrease of 1.07 pg/mL per 1-kg/m^2 increase), but showed no significant association with HIV serostatus, thyroid function, prolactin levels, or comorbidities. In HIV-positive group, the serum free testosterone levels were negatively associated with longer duration of HIV infection and positively associated with use of nucleoside reverse transcriptase inhibitors (NRTIs).

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Discussion:

This study is the largest Chinese Han cohort investigating hypogonadism in MSM. Primary hypogonadism accounts for 2.7% of MSM with HIV in our cohort, similar to rates observed in Italy. The lower prevalence of secondary hypogonadism (8.9%) in our study, compared to previous studies, may be due to better overall health, viral suppression, and exclusion of individuals on interfering medications. Our findings are consistent with the Multicenter AIDS Cohort Study (MACS), which also observed similar age-related declines in free testosterone levels in MSM with and without HIV. Using MSM without HIV as the control group may provide a more accurate comparison due to shared lifestyle behaviors. The positive association between NRTI use and serum free testosterone levels may be incidental due to the high prevalence of NRTI use (96.6%) in our study, which warrants further investigation. The limitations of our study include age discrepancy between the groups, single testosterone testing, and the exclusion of individuals on testosterone replacement therapy, which may lead to under- or over-estimation of true hypogonadism prevalence.

Conclusion:

We found that MSM with HIV had a higher prevalence of symptomatic hypogonadism than MSM without HIV in Taiwan, which could be attributed to age difference. Serum free testosterone levels were negatively correlated with age and BMI, but did not show a significant correlation with HIV serostatus.

KEYWORDS: Age; body mass index; human immunodeficiency virus; hypogonadism; testosterone

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Introduction

Early HIV diagnosis and treatment with combination antiretroviral therapy (ART) have led to enhanced survival rate in people with HIV (PWH) in Taiwan.[1,2] Recent studies have placed a growing emphasis on the quality of life among PWH, with particular interest in exploring endocrine issues.[3] The endocrine dysfunction associated with chronic HIV infection includes hypogonadism, growth hormone deficiency, hyperprolactinemia, and subclinical hypothyroidism.[3] Male hypogonadism is a well-documented yet often under-diagnosed health issue in PWH. The pathogenesis of HIV-related hypogonadism can be categorized into primary, secondary, and subclinical hypogonadism based on the specific sites of involvement within the hypothalamic-pituitary-gonadal axis.[4] Factors associated with primary hypogonadism in HIV-infected individuals include direct viral effects, the use of ART, chronic inflammation, and opportunistic infections.[5] Secondary hypogonadism, on the other hand, is linked to a broad spectrum of metabolic derangements, premature aging, poor health status, and various medications (Figure 1).[4]

Suggestive symptoms and signs of male hypogonadism include reduced sexual desire (libido) and activity, erectile dysfunction, breast discomfort, gynecomastia, low bone mineral density, hot flushes and sweats.[6] Other nonspecific symptoms and signs include decreased energy, depressed mood, poor memory, sleep disturbances,

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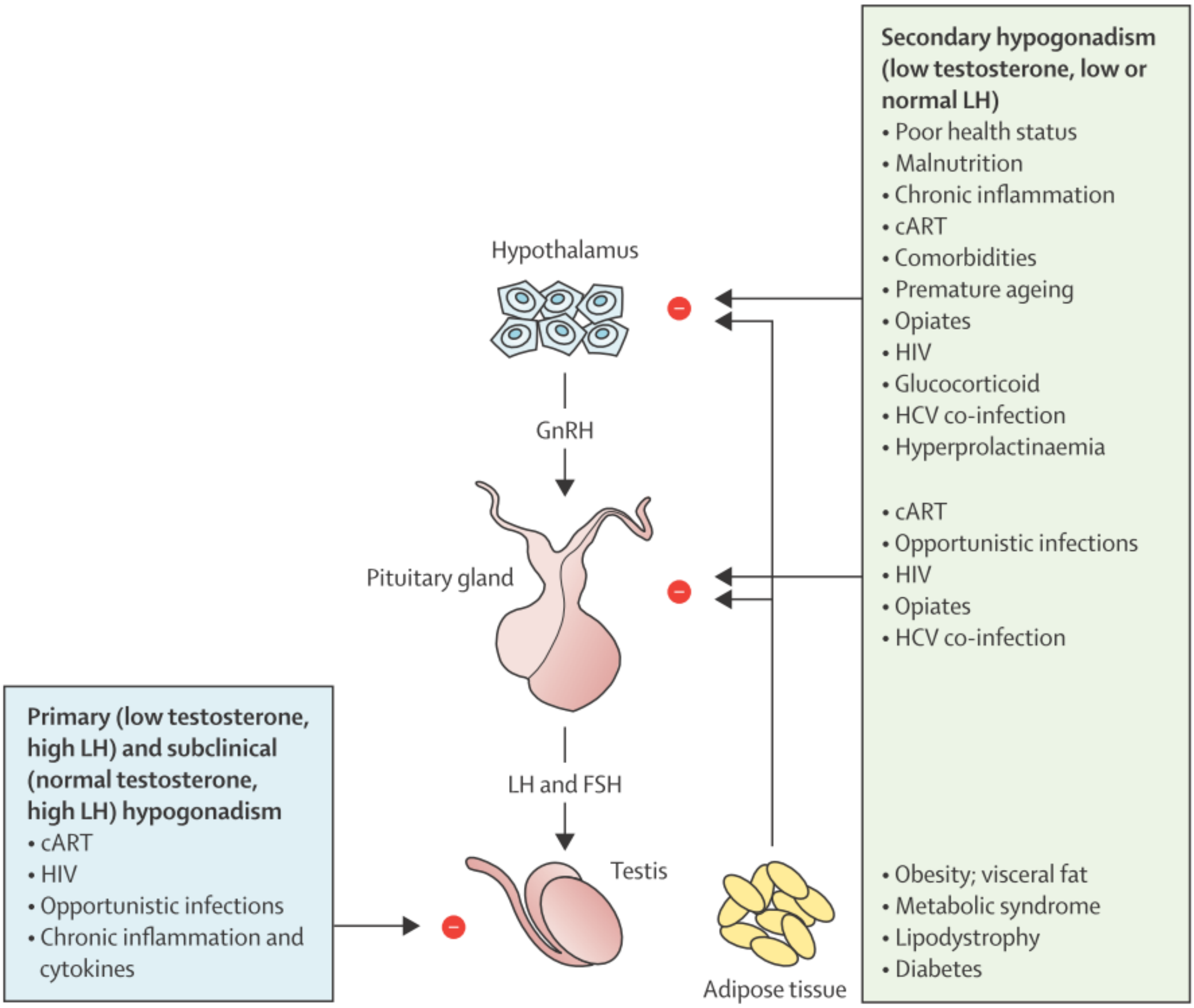

Figure 1. Pathogenesis HIV-related male hypogonadism

(Adapted from Maffezzoni F et al. Hypogonadism and bone health in men with HIV. *The lancet HIV* 2020;7:e782-e90[4])

cART, combined antiretroviral therapy; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HCV, hepatitis C virus; LH, luteinizing hormone.

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unexplained anemia, reduced muscle bulk and strength, as well as increased body fat.[6] Grinspoon et al used isotope analysis and dual-energy X-ray absorptiometry in 20 hypogonadal patients with AIDS-related wasting syndrome.[7] The result showed that lean body mass and physical activity significantly correlated with serum androgen levels.[7] A recent study suggested a modest correlation between serum testosterone levels and physical activity in general population, and whether this correlations also applied to PWH is unknown.[8] Another cross-sectional analysis revealed that HIV-positive individuals had lower free testosterone, higher sex-hormone binding globulin (SHBG) and more insulin resistance than those without HIV infection.[9] A large cohort study of 1359 HIV-infected men from Italy showed that low serum testosterone levels in HIV-infected men are associated bidirectionally with multimorbidity and poor health index, thus raising concern about testosterone supplement in this population.[10]

According to Endocrine Society Guidelines, the diagnosis of male hypogonadism includes the presence of symptoms and signs indicative of testosterone deficiency, alone with persistently and unequivocally low serum testosterone levels.[6] The Androgen Deficiency in Aging Men (ADAM) questionnaire, validated in the Chinese population, is widely utilized for screening symptoms associated with androgen deficiency (Table 1).[11] When the diagnosis of hypogonadism is confirmed, luteinizing hormone (LH) should be examined to differentiated between secondary and primary hypogonadism. Further

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potentially reversible functional causes and evaluation of other pituitary hormones should be considered in the setting of secondary hypogonadism (Figure 2).[6]

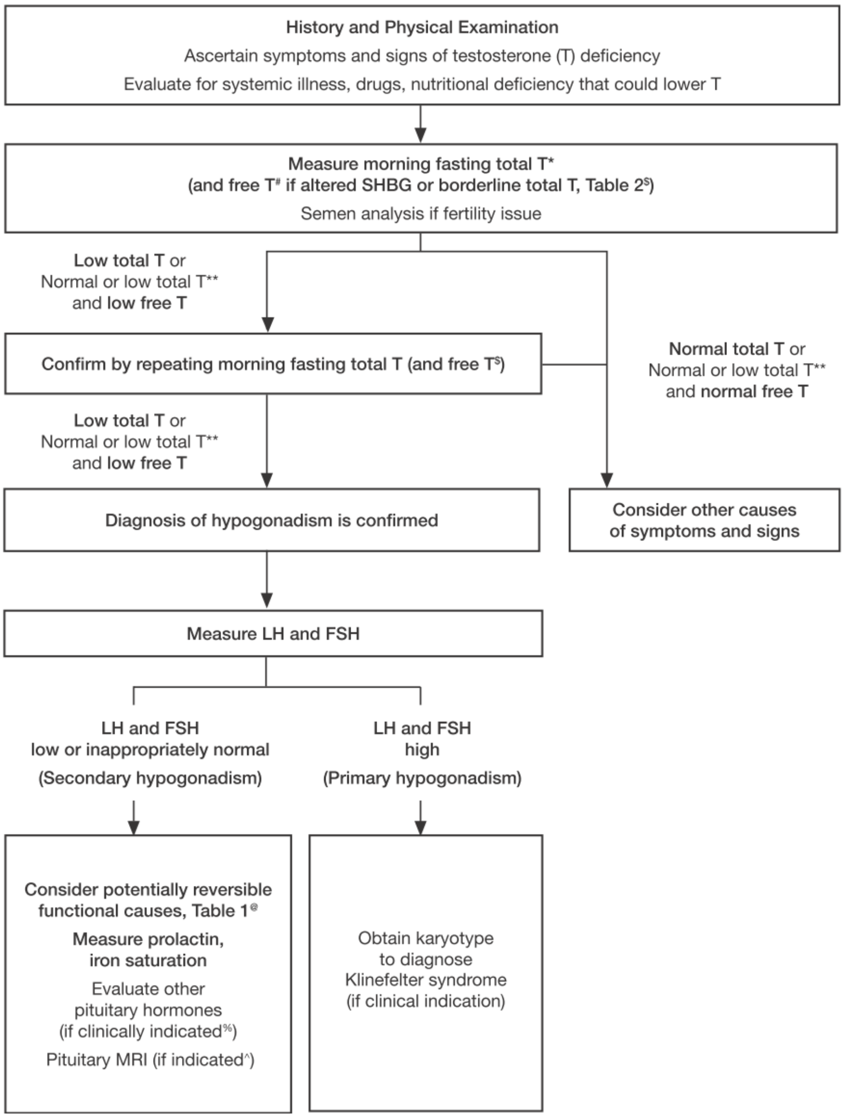

Figure 2. Algorithm of diagnosis of adult male hypogonadism

(Adapted from Bhasin et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2018;103:1715-44.[6])

FSH, follicle-stimulating hormone; LH, leutinizing hormone.

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Table 1. The Chinese version of ADAM questionnaire in the study

請問您最近一個月內是否有下列現象	
1.您是否有性慾(性衝動)降低的現象？	□是 □否
2.您是否覺得比較沒有元氣(活力)？	□是 □否
3.您是否有體力變差或耐受力下降的現象？	□是 □否
4.您的身高是否有變矮？	□是 □否
5.您是否覺得生活變得比較沒樂趣？	□是 □否
6.您是否覺得悲傷或沮喪？	□是 □否
7.您的勃起功能是否較不堅挺？	□是 □否
8.您是否覺得運動能力變差？	□是 □否
9.您是否在晚餐後會打瞌睡？	□是 □否
10.您是否有工作表現不佳的現象？	□是 □否
上述問題中，如果第 1 或 7 題回答「是」，或是其他八題有任三題回答「是」者，就需要進一步確認是否為睪固酮低下症患者。	

(Adapted from Chu et al. A short version of the ADAM Questionnaire for androgen deficiency in Chinese men. *J Gerontol A Biol Sci Med Sci* 2008;63:426-31.)

Before the era of combination ART, epidemiological studies have highlighted a high prevalence of hypogonadism, ranging from 30% to 50%, particularly among those with AIDS-related wasting syndrome.[7,12-14] Nowadays, with high rates of viral suppression among PWH engaged in care, the prevalence of hypogonadism has significantly decreased but remains relatively common among this population. As mentioned earlier, a large cohort study conducted in Italy revealed an estimated prevalence of biochemical hypogonadism of 16%, employing a serum total testosterone threshold of 300 ng/dL.[15] Another study in the United States (Multicenter AIDS Cohort Study, MACS) showed the comparable rates of biochemical hypogonadism between HIV-infected (9.3%) and those

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without HIV (7.2%).[16] However, inclusion of men on testosterone replacement therapy increased the prevalence substantially to 24% in the HIV-positive group.[16] Recent study in France reported male hypogonadism in 12.4% of patients with HIV, which is double the rate reported in the general population of the same age.[17] Follow-up 10 years study in the MACS cohort study showed that free testosterone levels decreased similarly with age regardless of HIV serostatus.[18]

Several potential limitations have been noted in prior studies regarding the prevalence of hypogonadism in PWH. A threshold of 10.4 nmol/L (300 ng/dL) for total testosterone levels was adopted by most studies. Nevertheless, conditions such as HIV infection and aging can elevate sex-hormone-binding globulin (SHBG), potentially resulting in normal total testosterone levels but low free testosterone levels. Conversely, obesity and diabetes can suppress hepatic SHBG production, leading to situations where free testosterone levels may be normal despite low total testosterone levels.[4,16,17] As a result, guidelines and recent expert panels suggest using free testosterone to diagnose hypogonadism in PWH, with a threshold of 220 pmol/L (63.5 pg/mL).[4,6] Another factor to consider is the diurnal variation in serum testosterone levels, which typically peak in the morning and decline towards the evening. Therefore, blood samples should ideally be collected in the morning and after overnight fasting.[6] Incorrect timing of blood sampling may result in misinterpretation of low testosterone levels. Furthermore, several studies

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lacked participants without HIV infection for comparison, posing challenges in accurately comparing testosterone levels between individuals living with HIV and those without the virus.

Testosterone is metabolized primarily via the liver by the enzyme cytochrome P450, family 3, subfamily A (CPY3A), including CYP3A4, CYP3A5 and CYP3A7, and the testosterone metabolites are excreted via the urine.[19,20] ARTs including all protease inhibitors, pharmacokinetic enhancers ritonavir, cobicistat, and one of the non-nucleoside reverse-transcriptase inhibitors (NNRTIs) efavirenz are inhibitor of CPY3A4.[21] On the other hand, NNRTI nevirapine are CPY3A4 inducers. Several studies have observed an increase in serum testosterone levels after initiation of ARTs in treatment naïve HIV patients.[22-24] However, the impact of different types of ARTs on serum testosterone levels had not been fully elucidated before. Protease inhibitors have been proposed to potentially interfere with testosterone metabolism, either increasing testosterone level by CPY3A4 inhibition or decreasing testosterone levels due to lipohypertrophy.[25,26] One study showed that in patients with low testosterone levels, those with elevated gonadotrophins had a higher frequency of NRTI use.[27]

Three meta-analyses of randomized controlled trials have indicated that in PWH, testosterone supplementation significantly increases lean body mass and muscle mass compared to placebo.[28-30] However, these findings are limited by the small number and

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heterogeneity of trials included, which could introduce bias into the results. Additional trials have demonstrated benefits of testosterone supplementation in improving mood, quality of life, sexual function, bone mineral density, and fatigue scores.[31-34] According to the 2018 Endocrine Society guidelines, short-term (3 to 6 months) testosterone therapy may be considered in HIV-infected men with low testosterone levels and weight loss to help induce and maintain body weight and lean mass gain, after excluding other causes of weight loss.[6] The increased screening for testosterone and diagnosis of late-onset hypogonadism, along with the promotion of various testosterone formulations and commercial advertising, has led to a notable increase in testosterone prescriptions, particularly among the HIV-positive population.[35,36] In the MACS cohort study, men who have sex with men (MSM) with HIV showed significantly higher usage of testosterone supplements compared to MSM without HIV (17% versus 5%).[37] Considering increasing cardiovascular risk in HIV seropositive population, it is prudent to discuss with patient about benefits and risk of testosterone supplement before prescribing testosterone in hypogonadal patients with HIV.[38-40]

Literature regarding androgen levels among PWH in Asia are limited, with the majority of studies on hypogonadism focusing on Caucasian populations. A Japanese study involving 25 treatment-naïve PWH reported that 52% had low free testosterone levels. However, information on symptoms related to hypogonadism was not provided in

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the study.[24] The objectives of our study were to determine the prevalence of low testosterone levels among men who have sex with men (MSM) with HIV presenting with symptoms suggestive of hypogonadism.[41] Additionally, we aimed to investigate the association between HIV infection and hypogonadism, and to explore the factors influencing serum free testosterone levels among HIV-positive individuals. We hypothesized that MSM with HIV in Taiwan would exhibit a prevalence of hypogonadism comparable to Caucasian populations, and higher than MSM without HIV infection. Additionally, we hypothesized that lower CD4 counts and HIV infection would be negatively associated with serum free testosterone levels.

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Methods

Study population

This study was a cross-sectional study. Enrollment took place between February 2021 and November 2022 at the infectious disease clinics of the National Taiwan University Hospital (NTUH) and NTUH Yunlin Branch. Adult MSM who were on stable antiretroviral therapy (ART) with suppressed plasma HIV-1 RNA levels (defined as <200 copies/ml) were included.[42] For comparison purposes, we also recruited MSM without HIV infection who were seeking anonymous HIV testing services and those participating in the government-funded pre-exposure prophylaxis (PrEP) program against HIV. Exclusion criteria encompassed individuals with evident causes of hypogonadism, such as documented pituitary, adrenal, or gonadal disorders unrelated to HIV infection, those who had undergone pituitary radiotherapy or systemic chemotherapy, individuals with acute illnesses, and those receiving medications that might disrupt the hypothalamic-pituitary-gonadal axis. To better evaluate the impact of age and CD4 counts on serum testosterone levels, we deliberately enrolled patients in 10-year age intervals and stratified CD4 counts into categories: normal (>500/mL), intermediate (350/mL ≤ CD4 < 500/mL), and advanced HIV (<350/mL).[43]

Data regarding clinical characteristics such as age, height, weight, and existing health conditions, was obtained through self-reported questionnaire interviews and

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electronic health medical record reviews (Table 2). Current smokers were those who had consumed at least one-hundred cigarettes in their lifetime, and who were still actively smoking at the time of enrollment in the study.[44] The presence of high blood pressure, diabetes, or dyslipidemia was noted through medical records and medication review. History of hepatitis B and hepatitis C was determined by detecting hepatitis B surface

Table 2. The baseline characteristics questionnaire in the study

年齡　　　　身高　　　　現在體重　　　　六個月前體重

慢性病史 □高血壓　□糖尿病　□高血脂　□B 型肝炎　□C 型肝炎　□肝硬化

□憂鬱症　□心臟疾病　□慢性腎臟衰竭　□甲狀腺疾病

□睡眠呼吸中止症候群　□其他

手術病史 □無　□有

抽菸 □無　□已戒

□目前仍在抽，10 年以下，每天____包

□目前仍在抽，10 年以上，每天____包

飲酒 □無　□幾乎每日一次　□每週 2-4 次

□約每週 1 次　□每月 1-2 次或更少　每次飲酒__________當量

(註: 每當量於每次 1 杯標準杯 4%啤酒 375ml or 小杯 40%烈酒 40 毫升 or 中杯 10%葡萄酒 150 毫升)

目前用藥

□ 只有在台大醫院的藥，包括

□ 吃其他醫院的藥，包括

□ 中草藥/保健食品，包括

□ 最近一年內或正在使用睪固酮製劑 (包括針劑/口服/凝膠)

□ 最近一年內或正在使用合成類固醇

□ 正在使用一般類固醇處方 (包括針劑/口服/皮膚藥膏)

□ 正在使用嗎啡類止痛藥物 (包括針劑/口服/貼片)

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antigen (HBsAg) and anti-hepatitis C antibody (anti-HCV), respectively. For PWH, details included duration of HIV infection, current CD4 count, and antiretroviral treatments. The study obtained approval from the NTUH Research Ethics Committee (protocols 202010105RIND and 202109144RINA), and all participants provided informed consent. Registration was completed on ClinicalTrials.gov (identifier NCT04760574).

Diagnosis of hypogonadism

Blood samples were collected in the early morning following an overnight fast to assess serum total testosterone, SHBG, LH, thyroid-stimulating hormone (TSH), free T4 and prolactin levels using the Access Chemiluminescent Immunoassay (Beckman Coulter, USA). Serum free testosterone levels were further determined using the Vermeulen equation.[4] Hyperthyroidism was defined as elevated serum free T4 levels (>1.12 ng/dL) with suppressed TSH levels. Subclinical hypothyroidism was characterized by elevated serum TSH levels (>5.33 uIU/mL) with normal serum free T4 levels (0.61-1.12 ng/dL). Hyperprolactinemia was identified as serum prolactin levels exceeding 20 ng/mL. The ADAM questionnaire was given to all study subjects to assess the symptoms and signs of hypogonadism.[11] A positive response was characterized as either answering "yes" to the sexual dysfunction question or affirming at least three other questions in the questionnaire

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(Table 1). Physical activity levels were evaluated using the Chinese version of International Physical Activity Questionnaire-Short Form (IPAQ-SF), categorizing activity into low, moderate, or high activity according to metabolic equivalent of task-minutes per week (Table 3).[45]

Biochemical hypogonadism was characterized by a morning fasting serum free testosterone level below 63.5 pg/mL.[4] Primary hypogonadism was identified by low free testosterone levels alongside elevated luteinizing hormone (LH) levels (cut-off value, 8.62 mIU/mL). Secondary hypogonadism was indicated by low serum free testosterone and subnormal or inappropriately normal serum LH levels. Subclinical hypogonadism manifested as normal serum free testosterone levels but elevated LH levels. Symptomatic hypogonadism was defined by a low serum free testosterone level along with a positive screening result on the ADAM questionnaire interview. Participants exhibiting low free testosterone levels were recommended to undergo repeated testosterone measurement in accordance with current guidelines.[6]

Statistical analysis

Clinical characteristics and demographic of the study participants were presented using descriptive statistics. Continuous variables with a normal distribution were presented as mean ± standard deviation, and unpaired t-tests were utilized for comparing

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Table 3. The Chinese version of International Physical Activity Questionnaire-Short Form (IPAQ-SF)

活動現況調查 ： 您在過去七天中花在身體活動的時間，包括工作、做家事、整理庭院／陽台、交通，及您在娛樂、運動等活動中所花的時間。就算您認為自己不愛動，也請您回答每一個問題。 您過去七天的身體活動與過去 3 個月的身體活動比較起來(請打勾) □1. 比較多　□2. 比較少　□3. 差不多(請繼續) 請回想過去七天中，所有您做過的費力活動。這些活動會讓您的身體感覺費力，呼吸比平常喘很多，但請只考慮那些一次您至少會持續 10 分鐘以上的身體活動。 1、過去七天中，您有多少天有做費力的身體活動？_______天 例如跑步、上山爬坡、持續性的快速游泳(不含慢游、玩水、泡水)、上樓梯、有氧舞蹈／運動、快速地騎腳踏車、打球(如網球單打、籃球、足球)、跳繩、重量訓練、搬運重物(大於 17 台斤／10 公斤)、或者是鏟土。 □　沒有做費力的身體活動　　　請跳答問題 3 2、您通常一天花多少時間在費力的身體活動上？ 一天______小時_______分鐘　　　　□　　不知道/不確定 回想過去七天中，您所有做過中等費力的活動。中等費力的活動表示：這些活動會讓您覺得身體有點費力，呼吸比平常喘些，但請只考慮那些您一次至少持續 10 分鐘以上的身體活動。 3、過去七天中，您有多少天有做中等費力的活動？_______天 例如：下山健走、用一般速度游泳、下樓梯、跳舞(不含有氧舞蹈、慢舞、國際標準舞或元極舞)、太極（不含外丹功)、用一般速度騎腳踏車、攜帶有點重的東西走路(例如買菜、背、抱小孩。有點重是指 7.5-15 台斤／4.5-9 公斤：例如二包 A4 的紙、二瓶家庭號鮮奶、一個小玉西瓜、三個帶皮鳳梨、五公斤的米、三個紅磚頭、七瓶玻璃罐的台灣啤酒或米酒、一箱 24 瓶易開罐飲料)、整理庭院／陽台、費力的家務(清洗窗戶、用手擦地、鋪床、手洗衣服、手工洗車)、或是網球雙打、羽毛球、桌球、排球、棒球？請不要將提輕物的走路算進去。 □　沒有做中等費力的活動　　　請跳答問題 5 4、您通常一天花多少時間在中等費力的活動上？ 一天______小時_______分鐘　　　　□　不知道/不確定 回想過去七天中，您花在走路上的時間有多久？包括工作、居家、和外出交通時的走路，以及您純粹為了娛樂、運動及休閒而花在走路（不含上下樓梯、爬山）上的時間。 5、過去七天中，您有多少天曾經走路持續 10 分鐘以上？ _______天 □　沒有走路持續 10 分鐘以上　　　請跳答問題 7 6、您通常一天花在走路上的時間有多久？ 一天______小時_______分鐘 □　不知道/不確定 最後一個問題是：過去七天的工作天中，您坐著的時間有多久？請將工作、居家、做功課及休閒的時間都算進去，包括坐在桌前、打電腦、拜訪朋友、吃飯、閱讀、坐著或斜躺著看電視，但請不要將睡著的時間算進去。 7、過去七天的工作天中，您一天坐著的時間有多久？ 一天______小時_______分鐘

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means between HIV-positive and HIV-negative groups. Continuous variables with a normal distribution were presented as mean ± standard deviation, and unpaired t-tests were utilized for comparing means between HIV-positive and HIV-negative groups. Continuous variables without a normal distribution were expressed as median (interquartile range), and between-group comparisons were conducted using the Mann-Whitney U test. Categorical variables were presented as absolute numbers and percentages, and Chi-square tests were employed to assess between-group differences. Statistical significance was defined as a two-tailed p-value of less than 0.05.

Stepwise regression analysis was performed to examine the association between serum free testosterone levels and various variables, including age, body-mass index (BMI), HIV serostatus, and comorbidities. Subgroup analysis within the HIV-positive group further explored associated factors such as duration of HIV infection, CD4 count, and antiretroviral therapy (ART). Three-way analysis of variance (ANOVA) was conducted to compare serum free testosterone levels across different levels of physical activity. All statistical analyses were carried out using Stata/SE 17.0 for Windows (StataCorp LP, College Station, TX).

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Results

Baseline characteristics

In this study, 447 MSM with HIV and 124 MSM without HIV were enrolled. Table 4 showed the distribution of study subjects according to age, HIV serostatus and current CD4 counts. The median age of MSM with HIV was significantly higher compared to MSM without HIV (41 years versus 29.5 years) (Table 5). MSM with HIV had significantly higher rate of chronic hepatitis, hypertension, hyperlipidemia and diabetes compared to HIV-negative group. After evaluating thyroid function and prolactin levels, one participant (0.2%) in the HIV-positive group had overt hyperthyroidism. MSM with HIV had significantly lower rates of subclinical hypothyroidism compared to MSM without HIV (0.5% versus 3.3%). Both groups had mild hyperprolactinemia in approximately 5% of participants, with levels ranging from 20 ng/mL to less than 50 ng/mL.

Table 4. Distribution of study subjects according to age, HIV serostatus and current CD4 counts.

Age (years)	HIV infection (patient number)			No HIV infection (patient number)
	CD4 < 350	350 ≤ CD4 < 500	CD4 ≥ 500	
20~29	10	26	45	62
30~39	32	32	59	46
40~49	32	42	55	13
≥ 50	29	36	48	3

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Table 5. Baseline characteristics of MSM with or without HIV

	MSM with HIV (N=447)	MSM without HIV (N=124)	*P*
Age (years)	41 [31 – 50]	29.5 [27 – 33]	< 0.001
BMI (kg/m^2)	23.7 [21.7 – 26.1]	23.7 [21.5 – 25.1]	0.401
Current smoker	125 (28.0%)	25 (20.2%)	0.081
Current CD4 (cells/µL)	482 [357 – 681]		
Duration of HIV infection (years)	8.5 [5.1 – 13.3]		
Types of current anti-retroviral therapy			
Nucleoside reverse-transcriptase inhibitors	432 (96.6%)	40 (32.3%)	
Non-nucleoside reverse-transcriptase inhibitors	33 (7.4%)		
Integrase inhibitors	428 (95.8%)		
Protease inhibitors	1 (0.2%)		
Co-infections			
Hepatitis B surface antigen positivity	75 (16.8%)	10 (8.1%)	0.016
Anti-hepatitis C antibody positivity	72 (16.1%)	2 (1.6%)	< 0.001
Systemic disease			
Hypertension	65 (14.5%)	3 (2.4%)	< 0.001
Diabetes	22 (4.9%)	1 (0.8%)	0.039
Hyperlipidemia	270 (60.4%)	6 (4.8%)	< 0.001
Chronic kidney disease	13 (2.9%)	0	0.058
Depression	17 (3.8%)	7 (5.7%)	0.366
Cardiovascular disease	16 (3.6%)	2 (1.6%)	0.267
Prolactin (ng/mL)	10.3 ± 0.3	10.6 ± 0.4	0.301
Hyperprolactinemia [a]	24 (5.5%)	6 (4.9%)	0.801
Overt hyperthyroidism [b]	1 (0.2%)	0	1.000
Subclinical hypothyroidism [c]	2 (0.5%)	4 (3.3%)	0.023

Continuous variables with a normal distribution are presented as mean ± standard deviation. Continuous variables not normally distributed are presented as median (interquartile range). Categorical variables are presented as absolute numbers (percentages).

[a] Hyperprolactinemia is defined as serum prolactin levels > 20 ng/mL

[b] Overt hyperthyroidism is defined as elevated serum free T4 with suppressed TSH levels.

[c] Subclinical hypothyroidism is defined as serum TSH levels > 5.33 uIU/mL, with normal serum free T4 levels.

Abbreviations: BMI, body mass index; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; MSM, men who have sex with men

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Among MSM with HIV, the median duration of HIV infection was 8.5 years, with a median CD4 count of 482 cells/μL, all achieving viral suppression (<200 copies/ml). The majority (89.7%) were receiving a regimen of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus an integrase inhibitor at the time of the survey. Emtricitabine plus tenofovir alafenamide (89.9%) was the most common NRTI combination, while bictegravir (55.7%) was the predominant integrase inhibitor. Other integrase inhibitors included cobicistat-boosted elvitegravir (30.4%) and dolutegravir (9.8%). A minority (6.9%) were prescribed the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine. In contrast, 40 MSM without HIV (32.3%) were on oral PrEP with coformulated tenofovir disoproxil fumarate/emtricitabine.

Serum androgen levels and prevalence of hypogonadism

Table 6 showed the serum androgen levels and prevalence of hypogonadism in all study subjects, categorized by HIV serostatus. The average serum total testosterone concentrations among MSM with HIV and those without were 4.63 ng/mL and 5.20 ng/mL, respectively. In terms of serum free testosterone, the mean levels were 98.8 pg/mL and 115.2 pg/mL for MSM with HIV and those without HIV, respectively. The mean serum SHBG levels in two groups were 33.4 nmol/L and 29.7 nmol/L, respectively (Table 6). The symptoms suggestive of hypogonadism, as identified by the ADAM questionnaire,

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were prevalent among participants, with 62.0% of MSM with HIV and 58.9% of MSM without HIV reporting positive symptoms. According to IPAQ-SF, the mean free testosterone levels for individuals with low, moderate, and high physical activity levels were 95.9 pg/mL, 104.2 pg/mL, and 104.6 pg/mL, respectively. No significant differences in serum free testosterone levels were observed across different categories of physical activity levels or HIV serostatus among the participants (Table 7).

Table 6. Serum testosterone levels and related symptoms across all age groups

	MSM with HIV (N=447)	MSM without HIV (N=124)	*P*
Total testosterone (ng/mL)	4.63 ± 1.41	5.20 ± 1.54	< 0.001
Free testosterone (pg/mL)	98.8 ± 31.2	115.2 ± 30.0	< 0.001
SHBG (nmol/L)	33.4 ± 17.1	29.7 ± 15.9	0.033
Albumin (g/dL)	4.33 ± 0.34	4.50 ± 0.26	< 0.001
Positive result on the ADAM questionnaire	276 (62.0%)	73 (58.9%)	0.524
Physical activity category according to IPAQ-SF			0.439
Low	58 (17.7%)	13 (13.1%)	
Moderate	153 (46.7%)	45 (45.5%)	
High	117 (35.7%)	41 (41.4)	
Prevalence of low free testosterone	52 (11.6%)	2 (1.6%)	0.001
Prevalence of symptomatic hypogonadism	37 (8.3%)	2 (1.6%)	0.009

Continuous variables with a normal distribution are presented as mean ± standard deviation. Categorical variables are presented as absolute numbers (percentages).

Abbreviations: ADAM, The Androgen Deficiency in Ageing Males; HIV, human immunodeficiency virus; IPAQ-SF, International Physical Activity Questionnaire - Short Form; SHBG, sex hormone-binding globulin.

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Table 7. Serum free testosterone levels across different physical activity levels according to IPAQ-SF among participants with HIV

Physical activity	Low N=52	Moderate N=146	High N=113	*P* value
Free testosterone (pg/mL)	95.9 ± 24.6	104.2 ± 31.1	104.6 ± 30.0	0.172

Table 8. Serum testosterone levels and prevalence of hypogonadism in participants aged <35 years

	MSM with HIV (N=150)	MSM without HIV (N=101)	*P*
Age (years)	29 [26-31]	29 [27-31]	0.057
BMI (kg/m^2)	21.1 [23.1-25.3]	21.3 [22.9-25.1]	0.776
Total testosterone (ng/mL)	4.95 ± 1.25	5.29 ± 1.53	0.050
Free testosterone (pg/mL)	114.4 ± 30.0	117.9 ± 30.5	0.368
SHBG (nmol/L)	27.8 ± 10.2	29.3 ± 15.0	0.340
Albumin (g/dL)	4.40 ± 0.30	4.54 ± 0.25	< 0.001
Prevalence of low free testosterone	7 (4.7%)	1 (1.0%)	0.149
Prevalence of symptomatic hypogonadism	5 (3.3%)	1 (1.0%)	0.406

Continuous variables not normally distributed are presented as median (interquartile range). Continuous variables with a normal distribution are presented as mean ± standard deviation. Categorical variables are presented as absolute numbers (percentages).

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; SHBG, sex hormone-binding globulin.

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The prevalence of biochemical hypogonadism among MSM with HIV was 11.6%, whereas it was 1.6% among MSM without HIV. Likewise, symptomatic hypogonadism was more prevalent in MSM with HIV (8.3%) compared to MSM without HIV (1.6%). The significant age discrepancies between MSM with and without HIV might contributed to the differences in serum testosterone levels and hypogonadism prevalence. Therefore, we conducted an additional analysis focusing on participants under 35 years old to compare these factors (Table 8). In this subpopulation, both MSM with and without HIV had a similar median age (29 years, *p*-value 0.06) and BMI. No significant differences were observed in two groups regarding serum free testosterone levels, SHBG, prevalence of biochemical and symptomatic hypogonadism (Table 8).

Figure 3 illustrates the gonadal status of 447 MSM with HIV based on a serum free testosterone threshold of 63.5 pg/mL and an LH threshold of 8.62 mIU/mL. Among MSM with HIV, secondary hypogonadism was the most prevalent form of biochemical hypogonadism, identified in 40 (8.9%) of participants, followed by subclinical hypogonadism (5.4%) and primary hypogonadism (2.7%) (Figure 3).

In HIV-positive group, those with biochemical hypogonadism were significantly older (median age, 48 versus 40 years, $P < 0.05$) and had a longer duration of HIV infection (median time 12.0 versus 8.3 years, $P < 0.05$), compared with those with normal free testosterone levels (Table 9). Additionally, HIV-positive hypogonadal subjects had a

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lower rate of NRTI use (86.5% versus 98.0%, P<0.05) and a higher rate of non-NRTI use (19.2% versus 5.82%, P <0.05). There were no statistically significant differences in the proportions of other comorbidities between those with and without biochemical hypogonadism.

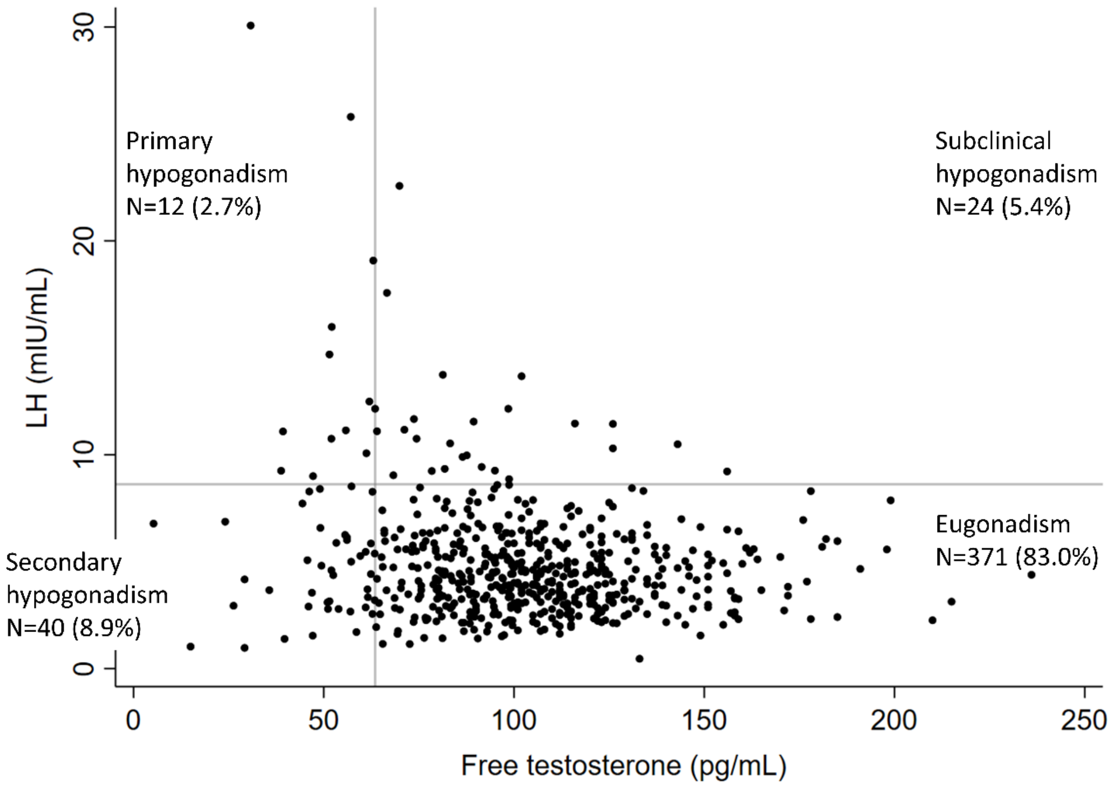

Figure 3. Gonadal status of 447 MSM with HIV according to serum free testosterone threshold of 63.5 pg/mL and LH threshold of 8.62 mIU/mL.

LH, luteinizing hormone; MSM, men who have sex with men

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Table 9. Comparisons between participants with and those without biochemical hypogonadism among participants with HIV

	With hypogonadism (N=52)	No hypogonadism (N=395)	*P*
Age (years)	48 [41 – 53.5]	40 [31 – 48]	**< 0.001**
BMI (kg/m^2)	24.4 [21.1 – 28.1]	23.7 [21.8 – 25.9]	0.334
Current smoker	19 (36.5%)	106 (26.8%)	0.143
Current CD4 (cells/μL)	524 [332 – 691]	481 [364 – 675]	0.785
Duration of HIV infection (years)	12.0 [8.2 – 15.4]	8.3 [4.8 – 12.9]	**< 0.001**
Types of current antiretroviral therapy			
Nucleoside reverse-transcriptase inhibitors	45 (86.5%)	387 (98.0%)	**<0.001**
Non-nucleoside reverse-transcriptase inhibitors	10 (19.2%)	23 (5.82%)	**0.002**
Integrase inhibitors	49 (94.2%)	379 (96.0%)	0.564
Protease inhibitors	0	1 (0.25%)	1.000
Co-infections			
Hepatitis B surface antigen positivity	13 (25.0%)	62 (15.7%)	0.091
Anti-hepatitis C antibody positivity	11 (21.2%)	61 (15.4%)	0.292
Systemic disease			
Hypertension	11 (21.2%)	54 (13.7%)	0.150
Diabetes	4 (7.69%)	18 (4.56%)	0.326
Hyperlipidemia	35 (67.3%)	235 (59.5%)	0.279
Chronic kidney disease	1 (1.92%)	12 (3.04%)	0.058
Depression	4 (7.69%)	13 (3.29%)	0.119
Cardiovascular disease	3 (5.77%)	13 (3.29%)	0.415
Thyroid disease	2 (3.85%)	4 (1.01%)	0.095

Continuous variables that are not normally distributed are presented as median (interquartile range).

Categorical variables are presented as absolute numbers (percentages).

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus

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Factors associated with serum free testosterone level

In multiple regression analysis was performed in all study subjects to evaluate clinical factors associated with serum free testosterone levels. The result showed that serum free testosterone levels negatively correlated with age and BMI (Table 10). No significant associations were found between serum free testosterone levels and HIV serostatus, thyroid function, prolactin levels, or comorbid conditions such as hypertension, hyperlipidemia, diabetes, or chronic hepatitis. On the other hand, serum SHBG levels positively correlated with increased age, HBsAg and anti-HCV positivity, and negatively correlated with body mass index, hypertension, and hyperlipidemia. Additionally, we used linear regression models to predict serum free testosterone levels in relation to age. No statistically significant differences were observed in the rate of free testosterone decline associated with aging between MSM with HIV and MSM without HIV (Figure 4).

Among MSM with HIV, serum free testosterone levels exhibited a significant decline with advancing age, higher BMI, and longer duration of HIV infection (Table 11). Additionally, there was a positive association observed between serum free testosterone levels and the use of NRTIs. Conversely, no significant correlations were found between serum free testosterone levels and CD4 count, thyroid function, prolactin levels, or comorbidities such as hypertension, hyperlipidemia, diabetes, and viral hepatitis B or C

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serostatus. Similar to the findings across all study participants, serum SHBG levels in MSM with HIV increased significantly with age and were positively associated with the presence of HBsAg and anti-HCV, while displaying a negative association with BMI, hypertension, and hyperlipidemia.

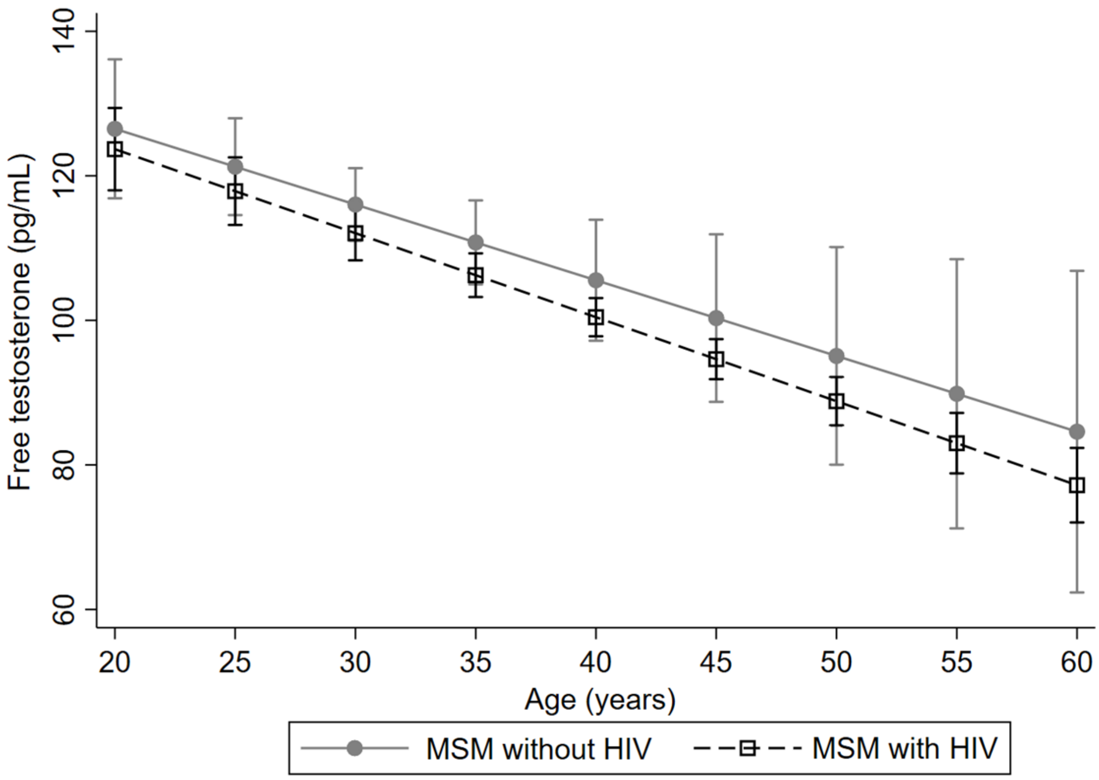

Figure 4. Age-predicted serum free testosterone decline in MSM with or without HIV. P value for interactions between HIV serostatus and age was 0.774.

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Table 10. Factors associated with serum free testosterone levels (left column) and serum SHBG levels (right column) in all subjects via simple and multiple linear regression models. (n = 554)

Variables	Free testosterone (pg/mL)				SHBG (nmol/L)			
	Unadjusted model[a]		Adjusted model[b]		Unadjusted model[a]		Adjusted model[b]	
	Regression coefficient	*P value*	Regression coefficient	*P value*	Regression coefficient	*P value*	Regression coefficient	*P value*
HIV serostatus[c]	-16.44	< 0.001	-4.32	0.172	3.66	0.033	0.65	0.720
Age (years)	-1.24	< 0.001	-1.14	< 0.001	0.42	< 0.001	0.51	< 0.001
BMI (kg/m^2)	-1.43	< 0.001	-1.07	< 0.001	-1.24	< 0.001	-1.09	< 0.001
Current smoker[d]	0.51	0.866			2.61	0.105		
HBsAg positivity[e]	-13.42	< 0.001			12.34	< 0.001	9.16	< 0.001
Anti-HCV positivity[e]	-8.60	0.029			5.23	0.013	5.18	0.009
Hypertension[f]	-19.29	< 0.001			-1.13	0.604	-5.48	0.014
Diabetes[f]	-13.99	0.038			-0.48	0.893		
Hyperlipidemia[f]	-15.11	< 0.001			-1.88	0.186	-5.33	< 0.001
Chronic kidney disease[f]	-10.02	0.261			-2.06	0.665		
Free T4 (ng/dL)	16.57	0.050			-3.18	0.484		
Prolactin (ng/mL)	0.13	0.579			-0.15	0.224		

[a]Free testosterone (left column) and SHBG (right column) as dependent variable, other clinical factors as independent variables, using simple linear regression analysis.

[b]Free testosterone (left column) and SHBG (right column) as dependent variable, other clinical factors as independent variables, using multiple linear regression analysis and forward stepwise selection. HIV serostatus was included in the model as a forcing variable.

[c]HIV serostatus: 0, no HIV infection; 1, positive HIV infection

[d]Current smoker: 0, not active smoking currently; 1, smoking at least 100 cigarettes during lifetime and were still actively smoking at the time of study enrollment.

[e]HBsAg positivity, anti-HCV positivity: 0, no; 1, yes

[f]Comorbidities: 0, no; 1, yes. Chronic kidney disease defined as an estimated glomerular filtration rate less than 60 ml/min/1.73m^2

Abbreviations: Anti-HCV, anti-hepatitis C antibody; BMI, body mass index; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; SHBG, sex hormone-binding globulin.

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Table 11. Factors associated with serum free testosterone levels (left column) and serum SHBG levels (right column) in MSM with HIV via simple and multiple linear regression models. (n = 420)

Variables	Free testosterone (pg/mL)				SHBG (nmol/L)			
	Unadjusted model[a]		Adjusted model[b]		Unadjusted model[a]		Adjusted model[b]	
	Univariate coefficient	*P value*	Multivariate coefficient	*P value*	Univariate coefficient	*P value*	Multivariate coefficient	*P value*
Age (years)	-1.18	< 0.001	-0.89	< 0.001	0.43	< 0.001	0.54	< 0.001
BMI (kg/m^2)	-1.24	0.001	-1.03	0.003	-1.16	< 0.001	-0.96	< 0.001
Current smoker[c]	1.50	0.650			2.62	0.147		
Current CD4 (cells/μL)	0.004	0.468			-0.006	0.045		
Duration of HIV infection (years)	-1.79	<0.001	-0.84	0.002	0.45	0.001		
NRTI use[d]	24.57	0.003	28.0	<0.001	2.62	0.561		
NNRTI use[d]	-14.04	0.013			-2.97	0.338		
II use[d]	3.67	0.616			2.33	0.562		
HBsAg positivity[e]	-12.75	0.001			10.23	< 0.001	7.04	< 0.001
Anti-HCV positivity[e]	-5.26	0.191			4.95	0.025	5.23	0.012
Hypertension[f]	-16.67	< 0.001			-1.22	0.595	-5.13	0.034
Diabetes[f]	-12.14	0.075			-0.70	0.851		
Hyperlipidemia[f]	-10.85	< 0.001			-4.29	0.009	-5.43	0.001
Chronic kidney diseases[f]	-6.41	0.466			-2.83	0.558		
Free T4 (ng/dL)	18.66	0.041			-4.01	0.429		
Prolactin (ng/mL)	0.13	0.588			-0.17	0.214		

[a]Free testosterone (left column) and SHBG (right column) as dependent variable, other clinical factors as independent variables, using simple linear regression analysis.

[b]Free testosterone (left column) and SHBG (right column) as dependent variable, other clinical factors as independent variables, using multiple linear regression analysis and forward stepwise selection.

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[c]Current smoker: 0, not active smoking currently; 1, smoking at least 100 cigarettes during lifetime and were still actively smoking at the time of study enrollment.

[d]NRTI use, NNRTI use, II use: 0, no; 1: yes

[e]HBsAg positivity, anti-HCV positivity: 0, no; 1, yes

[f]Comorbidities: 0, no; 1, yes. Chronic kidney disease defined as an estimated glomerular filtration rate less than 60 ml/min/1.73m^2

Abbreviations: Anti-HCV, anti-hepatitis C antibody; BMI, body mass index; CD4, cluster of differentiation 4; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IIs, integrase inhibitors; MSM, men who have sex with men; NNRTIs, Non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse-transcriptase inhibitors; PIs, protease inhibitors; SHBG, sex hormone-binding globulin.

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Discussion

This study represents the largest Chinese Han cohort to date investigating the clinical manifestations and prevalence of hypogonadism among MSM. We followed current practice guidelines by employing morning fasting free testosterone levels as the diagnostic criterion for hypogonadism.[6] Our findings revealed that MSM with HIV had a symptomatic hypogonadism prevalence of 8.3%, whereas MSM without HIV had a prevalence of 1.6%. MSM with HIV exhibited comparable age-predicted serum free testosterone levels and age-related declines in free testosterone compared to MSM without HIV infection. Our analysis further identified older age, higher BMI, and longer duration of HIV infection as factors associated with lower serum free testosterone levels. Additionally, HBsAg and anti-HCV positivity correlated with elevated serum SHBG levels, though they did not significantly impact free testosterone levels. Similarly, hypertension and hyperlipidemia were associated with reduced serum SHBG levels but did not significantly affect free testosterone levels.

Comparison of findings from our study with previous literature

In our study, the prevalence of hypogonadism in MSM with HIV was lower compared to the that reported in the literature, which ranged from 9.3% to 52% (Table 12).[16,17,24,27,41] The variability in hypogonadism prevalence across these studies could be resulted from differences in the age distribution of their respective populations and variations in the definitions used for hypogonadism. Our study population exhibited comparable median age and BMI to the France

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study, which reported a hypogonadism prevalence of 12% among MSM with HIV.[17] Another potential factor contributing to the lower prevalence of hypogonadism could be the improved overall health status observed in MSM with HIV. Research has indicated an inverse correlation between serum testosterone levels and the number of comorbidities and frailty index.[10] Our study population had a lower prevalence of viral hepatitis and chronic metabolic diseases compared to earlier studies, suggesting a generally better health status among Taiwanese participants.

Table 12. Comparing prevalence of hypogonadism among people with HIV in our study and previous literatures

	Our study[41]	**Italy, 2011[15]**	**United States, 2014[16]**	**France, 2017[17]**
Number of study subjects	HIV+ 442 HIV- 122	HIV + 1325	HIV+ 364 HIV- 166	HIV+ 113
Median age of study subjects (years)	HIV+ 41.2 HIV- 31.0	45	HIV+ 51.6 HIV- 48.1	41
Cut-off value of hypogonadism	Free T < 63.5 pg/mL	Total T < 300 ng/dL	Free T < 50 pg/mL or Total T < 300 ng/dL	Free T < 70 pg/mL
Biochemical hypogonadism	HIV+ 8.14% HIV- 1.64%	HIV+ 16%	HIV+ 9.3% HIV- 7.2%	HIV+ 12.5%
Symptomatic hypogonadism	HIV+ 5.88% HIV- 1.64%	N/A	N/A	N/A

Abbreviations: Free T, free testosterone; HIV, human immunodeficiency virus; N/A, not available; Total T, total testosterone

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Association between hypogonadism and HIV serostatus

Contrary to our initial hypothesis, the study did not identify a significant association between serum free testosterone levels and HIV serostatus. In previous literature, HIV infection might result in primary hypogonadism due to interference with testosterone production by direct viral effect or chronic inflammation.[4] The prevalence of primary hypogonadism was 2.7% in our HIV-positive cohort, which is comparable to the prevalence observed in the Italian cohort.[15] On the other hand, the pathogenesis of secondary hypogonadism is multifactorial, as any factors could interfere with hypothalamic-pituitary-gonadal axis (Figure 1).[4] Due to recent improved general health among people with HIV in Taiwan, with suppressed viral loads, we believed this could contribute to the lower prevalence of secondary hypogonadism (8.9%) in our cohort. Limited studies have enrolled MSM without HIV participants to investigate the prevalence of hypogonadism in MSM with HIV. Our results were similar to the findings from the MACS study, as both showed a comparable rate of free testosterone decline with aging among the two groups.[16,18] It's noteworthy that our study included MSM without HIV as the control group, possibly sharing similar lifestyle behaviors with MSM with HIV compared to the general population. Additionally, the overall health status of MSM with HIV may have improved over time compared to participants in the MACS study, conducted over a decade ago.

Other factors associated with serum free testosterone levels

Whether the regimen of ART effects to serum free testosterone levels is still unclear. We

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incidentally found a positive association between NRTIs use and serum free testosterone levels. Due to the highly prevalent use of NRTIs (96.6%) in our study, we further examined the residual 15 subjects who did not receive NRTIs. These participants all received a combination regimen of dolutegravir and rilpivirine. Nonetheless, we could not find the association between these two ARTs and low serum testosterone levels in the literature. These medications had not been shown to interfere with testosterone metabolism, either. Table 13 showed the additional analysis of serum free testosterone in participants using different numbers of NRTIs. In the HIV-positive group, there were no significant differences in serum free testosterone levels between those using no NRTIs and those using one NRTI. Similarly, in the HIV-negative group, serum free testosterone levels did not differ between participants using and not using PrEP (a combination of two NRTIs). We hypothesized unidentified confounding factors might exist in MSM with HIV receiving fewer than two NRTIs. Physicians may switch from more common ART regimens to second-line treatments due to drug resistance, drug interactions or other comorbidities. These comorbidities, rather than the ART regimen itself, could potentially impact serum free testosterone levels. On the other hand, a recent study revealed that among virally suppressed MSM with HIV, switch to regimen of bictegravir, emtricitabine and tenofovir alafenamide relieved HIV-associated symptoms.[46] In our study, 55% of MSM with HIV received this regimen.

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Table 13. The effect of using nucleoside reverse transcriptase inhibitors on serum free testosterone levels

In MSM with HIV				
	No NRTI (n=15)	One NRTI (n=14)	Two NRTIs (n=218)	*P*
Free testosterone (pg/mL)	75.0 ± 27.4	73.0 ± 33.2	100.5 ± 30.6	0.040
In MSM without HIV				
	No NRTI (n=84)		Two NRTIs (n=40)	*P*
Free testosterone (pg/mL)	114.9 ± 28.9		115.9 ± 32.4	0.864

HCV infection had been shown to increase serum SHBG and decrease free testosterone levels.[47,48] Fewer studies examined the impact of HBV infection on serum free testosterone levels.[49] Our study found that individuals with HBsAg and anti-HCV positivity had significantly elevated serum SHBG levels among HIV-positive group, yet this did not affect free testosterone levels. This observation aligns with previous findings indicating that co-infection with viral hepatitis is not predictive of serum androgen levels.[10,15] In patients with obesity, inflammatory cytokines and metabolic disorders may reduce gonadotropin frequencies, which result in lower free testosterone and SHBG production.[50] Our study revealed a significant negative correlation between BMI and both serum SHBG and free testosterone levels in MSM with HIV. Prior research has also highlighted BMI as a negative predictor for serum testosterone levels.[15] In contrast, during the pre-ART era, there was a positive correlation between free testosterone levels and body weight in patients with HIV wasting syndrome.[7] This suggests that

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there may be different mechanisms involved in the pathogenesis of hypogonadism between HIV patients with wasting syndrome and those with obesity.

Hyperprolactinemia is known to interfere with gonadotropin-releasing hormones and is associated with secondary hypogonadism.[6] In our study, 23 participants (4.5%) exhibited mild increases in serum prolactin levels, ranging from 20 to 50 ng/mL. We explored whether these individuals were at higher risk of developing male hypogonadism. However, in multiple linear regression models, neither serum prolactin levels nor the presence of hyperprolactinemia correlated with serum free testosterone levels. Furthermore, the prevalence of hypogonadism remained similar regardless of whether participants with mild hyperprolactinemia were excluded or included in the analysis (Table 13). Therefore, it was appropriate to include these individuals with mild hyperprolactinemia in our study. On the other hand, primary hypothyroidism has been noted to link with hypogonadism due to its impact on reducing LH response to gonadotropin-releasing hormone.[51] In our study, where 1% of study subjects had subclinical hypothyroidism and none had primary hypothyroidism, serum free T4 levels did not show an association with free testosterone levels in the multiple regression analyses.

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Table 14. The prevalence of symptomatic hypogonadism with and without participants with hyperprolactinemia

Prevalence of symptomatic hypogonadism	MSM with HIV	MSM without HIV	*P*
People with mild hyperprolactinemia included (as in Table 2)	37/447 (8.3%)	2/124 (1.6%)	0.009
People with mild hyperprolactinemia excluded	35/423 (8.3%)	2/118 (1.7%)	0.012

The utility of screening stools in HIV-related hypogonadism

ADAM questionnaire is a widely employed and convenient tool for screening male hypogonadal symptoms. In community-based Chinese men, the ADAM questionnaire screening for low serum free testosterone levels had a high sensitivity of 88% but low specificity of 32%.[11] We performed analysis on serum free testosterone levels and prevalences of biochemical hypogonadism according to ADAM questionnaire results (Table 14). Among MSM with HIV, those with positive ADAM result were significantly older. There were no significant differences in serum free testosterone levels and prevalences of biochemical hypogonadism between participants with positive and those with negative ADAM result. The sensitivity and specificity of ADAM questionnaire in predicting low free testosterone were 71% and 39%, respectively. The lower sensitivity in our cohort compared with previous study in China implied that there a significant proportion of MSM with HIV had low serum testosterone levels but without hypogonadal symptoms.

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Table 15. Serum free testosterone levels and prevalences of biochemical hypogonadism in MSM with HIV according to ADAM questionnaire results

MSM with HIV	Positive ADAM result N=276	Negative ADAM result N=169	P
Age	43 [34 – 50]	35 [29 – 46]	< 0.001
BMI	23.8 [21.7 – 25.8]	23.7 [21.8 – 26.3]	0.463
Free testosterone (pg/mL)	96.9 ± 31.1	102.5 ± 30.5	0.062
Biochemical hypogonadism	27 (9.8%)	11 (6.5%)	0.230

Limitations of our study

There are several limitations to our study, and the results should be interpreted cautiously. Firstly, there was a significant age discrepancy between the two groups of participants. Enrolling MSM without HIV who were similar in age to MSM with HIV was challenging in our study setting. This difficulty arose because participants from the government-funded PrEP program, which included MSM under 35 years of age, and those utilizing anonymous HIV testing services tended to be younger compared to MSM with HIV. To solve this problem, multiple regression analysis was performed to adjust for age (Table 10). Additionally, we conducted a subgroup analysis to compare serum testosterone levels and the prevalence of hypogonadism in MSM with and those without HIV within the same age stratification. The result showed no statistically significant differences between MSM with and MSM without HIV regarding serum free testosterone levels and prevalence of hypogonadism (Table 8). Secondly, as serum testosterone levels exhibit physiological daily variations, relying on the single testosterone test to diagnose hypogonadism could lead to an overestimation of the true

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prevalence of hypogonadism. In our study, 18 out of 54 participants with low free testosterone levels underwent repeated measurement. The reasons for significant loss to follow-up could be that these participants were not experiencing bothersome symptoms of hypogonadism and might not have taken their low testosterone levels seriously, thus lacking motivation to return for another testosterone measurement. Nevertheless, since most epidemiological studies on hypogonadism in MSM with HIV have utilized single testosterone measurements, our findings can be reasonably compared with those of previously published studies.[15,16,24] However, conducting a longitudinal follow-up study of participants with subnormal free testosterone levels would be warranted. Thirdly, our study excluded individuals undergoing testosterone replacement therapy, potentially leading to an underestimation of the actual prevalence of hypogonadism among MSM populations. These exclusions were necessary because we couldn't verify their diagnosis and prior serum testosterone levels before starting therapy. Moreover, existing literature indicates that testosterone prescriptions frequently deviate from guidelines, suggesting that some of these patients may not genuinely have hypogonadism.[35] Lastly, given the stigma associated with HIV infection, some participants may have declined to participate in the study, particularly those recruited from anonymous HIV testing services, citing privacy concerns. This potential selection bias could impact the estimated prevalence of hypogonadism.

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Perspective and Conclusion

Our cross-sectional study delineated some important factors associated with male hypogonadism in MSM with HIV population. We noted that in HIV-positive obese individuals in our study, 18.3% had low free testosterone levels. From the clinical perspective, this subgroup may indicate a particular population that could benefit from screening for male hypogonadism. In the future, conducting longitudinal follow-ups of high-risk populations could be a relatively cost-effective approach to explore causal relationships among serum testosterone levels, symptoms, and aging. The duration of HIV infection represents a significant clinical factor associated with free testosterone levels, independent of age. Future studies could also investigate additional parameters such as the interval between diagnosis and treatment initiation, initial CD4 counts, and history of opportunistic infections.

In conclusion, our study revealed a low prevalence of hypogonadism (8.3%) among MSM with HIV in Taiwan, with secondary hypogonadism being the predominant form. Serum free testosterone levels were negatively associated with age, BMI and duration of HIV infection. No significant correlation was observed with HIV serostatus. Furthermore, both MSM with HIV and those without showed a comparable age-related decline in serum free testosterone levels.

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