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# Correlation of Gonadal Hormone Levels in Hypogonadism with CD4 Count in HIV Male Patients.

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## Abstract

***Background:*** Hypogonadism is a frequently encountered endocrine complication among men living with human immunodeficiency virus (HIV). Its pathogenesis may involve chronic inflammation, immunosuppression, systemic illness, opportunistic infections, altered sex hormone-binding globulin and antiretroviral therapy. The relationship between gonadal hormones and CD4 count remains inconsistent across studies. ***Aim:*** To assess the correlation between gonadal hormone levels and CD4 count among male HIV patients with hypogonadism. ***Materials and Methods:*** This hospital-based analytical cross-sectional study included 80 male HIV patients aged 18-70 years who attended or were admitted to hospitals affiliated with tertiary care centre. Sociodemographic, clinical and treatment-related information was recorded using a structured proforma. Morning serum free testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were measured, and CD4-positive T-lymphocyte counts were obtained. Participants were classified as eugonadal or as having primary or secondary hypogonadism according to their testosterone and gonadotropin profiles. Quantitative variables were summarized using mean and standard deviation, while categorical variables were presented as frequencies and percentages. Group comparisons were performed using independent-samples t tests and one-way analysis of variance. A two-tailed p value <0.05 was considered statistically significant. ***Results:*** Of the 80 participants, 49 (61.3%) were eugonadal and 31 (38.8%; 95% CI: 28.8%-49.7%) had hypogonadism. Primary hypogonadism was present in 23 (28.8%) participants and secondary hypogonadism in 8 (10.0%). Among hypogonadal participants, primary hypogonadism accounted for 74.2% and was significantly more frequent than secondary hypogonadism (p=0.011). Mean free testosterone was 10.25 (3.68) pg/mL in the eugonadal group, 3.37 (1.41) pg/mL in primary hypogonadism and 3.71 (1.76) pg/mL in secondary hypogonadism (F≈47.18, p<0.001). Differences in FSH (p=0.123) and LH (p=0.326) were not statistically significant. The overall mean CD4 count was 459 (346) cells/$mm^3$. Mean CD4 count was lower in participants with hypogonadism than in eugonadal participants 403 (323) versus 494 (358) cells/$mm^3$ with a mean difference of 91 cells/$mm^3$ (95% CI: −62 to 244; p=0.238). CD4 counts did not differ significantly across the three gonadal-status groups (F≈0.80, p=0.456; $\eta^2$≈0.02). ***Conclusion:*** Hypogonadism affected more than one-third of the male HIV patients, with primary hypogonadism being the predominant type. Free testosterone differed significantly according to gonadal status, whereas FSH and LH did not. Although hypogonadal participants had lower mean CD4 counts, no statistically significant association was found between gonadal status and CD4 count. Hypogonadism in men living with HIV appears to be multifactorial and should be assessed using both clinical features and appropriately timed hormonal measurements.

**Keywords:** HIV infection; hypogonadism; CD4 count.



## INTRODUCTION

Human immunodeficiency virus (HIV) infection remains a major global health concern, with approximately 41 million people living with HIV worldwide at the end of 2025. The widespread availability of effective antiretroviral therapy (ART) has transformed HIV infection into a manageable chronic condition, substantially improving survival among people living

with HIV [1]. Consequently, greater attention is now being directed toward long-term metabolic and endocrine complications that influence morbidity and quality of life. Hypogonadism is one of the most frequently encountered endocrine disorders among HIV-infected men and is characterized by inadequate testosterone production, impaired spermatogenesis, or both. Its prevalence varies according to the population studied, stage of HIV infection, ART exposure, diagnostic criteria and method used for testosterone assessment; contemporary studies have reported prevalence estimates ranging from approximately 13% to 40% among men living with HIV [2].

The pathogenesis of hypogonadism in HIV is multifactorial and may involve direct effects of chronic infection, systemic inflammation, opportunistic infections, malnutrition, weight loss, increased sex hormone-binding globulin, testicular dysfunction, hypothalamic-pituitary involvement, comorbidities and adverse effects of medications. Both primary hypogonadism, characterized by low testosterone with elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and secondary hypogonadism, characterized by low testosterone with low or inappropriately normal gonadotropin levels, may occur [2,3].

Clinical manifestations include reduced libido, erectile dysfunction, fatigue, loss of muscle mass, decreased bone mineral density, mood disturbances, infertility and impaired quality of life. The diagnosis should be based on compatible clinical manifestations together with consistently reduced morning testosterone concentrations; measurement of LH and FSH helps differentiate primary from secondary hypogonadism [4]. CD4-positive T-lymphocyte count is an important indicator of immune function and HIV disease severity. Advanced immunosuppression, particularly a CD4 count below 200 cells/mm$^3$, may be accompanied by systemic illness and endocrine dysfunction. Earlier studies reported an association between low testosterone levels or hypogonadism and reduced CD4 counts, although findings in ART-treated populations have not been uniform [3,5].

Evaluating gonadal hormones in relation to CD4 count may therefore help determine whether worsening immunosuppression is associated with disruption of the hypothalamic-pituitary-gonadal axis. Early recognition of hypogonadism is clinically important because many symptoms may otherwise be attributed to HIV infection, ART, psychological illness or chronic fatigue. The present study was undertaken to estimate gonadal hormone levels, determine the pattern of hypogonadism and assess their correlation with CD4 count among adult male patients living with HIV.

**AIM**

To assess the correlation between gonadal hormone levels and CD4 count among male HIV patients with hypogonadism.

**OBJECTIVES**

1. To estimate serum free testosterone, LH and FSH levels among adult male patients living with HIV.
2. To determine the prevalence and type of hypogonadism among male HIV patients.
3. To correlate gonadal hormone levels and hypogonadal status with CD4 count among the study participants.

## MATERIALS AND METHODS

**Source of Data**

The study participants were recruited from adult male patients diagnosed with HIV who attended the outpatient department or were admitted to the Department of Medicine of hospitals affiliated with Bangalore Medical College and Research Institute (BMCRI), Bengaluru. Relevant clinical and treatment-related information was supplemented from ART-centre records and hospital case records wherever required.

**Study Design**

A hospital-based analytical cross-sectional study was conducted.

**Study Location**

The study was carried out in the Department of Medicine and its affiliated hospitals under tertiary care centre, in coordination with the ART centre and the institutional departments of Biochemistry and Microbiology/Pathology.

**Study Duration**

The study was conducted over a period of 12 months.

**Sample Size**

A total of 80 adult male HIV patients were included. The sample size was estimated using a previously reported prevalence of hypogonadism of 29.4%, a 95% confidence level and an absolute precision of 10%:
The calculated sample size was approximately 79 and was rounded to 80 participants.

**Inclusion Criteria**

1. Male patients aged 18-70 years were included.
2. Patients with confirmed HIV infection, irrespective of ART status or treatment regimen, were included.
3. Patients who provided written informed consent were included.
4. Patients for whom CD4 count and gonadal hormone measurements could be performed during the study period were included.

**Exclusion Criteria**

1. Patients who declined or were unable to provide informed consent were excluded.
2. Patients younger than 18 years or older than 70 years were excluded.
3. Patients receiving testosterone replacement, anabolic steroids, antiandrogens or other medications known to substantially alter gonadal hormone levels were excluded.
4. Patients with known pituitary or hypothalamic disease, testicular surgery or trauma, congenital gonadal disorders or previously diagnosed hypogonadism were excluded.
5. Patients with hypothyroidism, adrenal insufficiency or hyperprolactinaemia were excluded.
6. Patients with acute critical illness or an active severe opportunistic infection at the time of hormone estimation were excluded because these conditions could transiently suppress testosterone levels.

**Procedure and Methodology**

Approval was obtained from the Institutional Ethics Committee of BMCRI, and the necessary administrative permission was obtained from the Karnataka State AIDS Prevention Society and the respective ART centre. Eligible participants were informed about the purpose, procedures, potential benefits and confidentiality provisions of the study. Written informed consent was obtained before enrolment.

A detailed history was recorded regarding age, duration of HIV infection, duration and regimen of ART, treatment adherence, previous opportunistic infections, comorbidities, medication use, smoking and alcohol consumption. Symptoms suggestive of androgen deficiency, including reduced libido, erectile dysfunction, fatigue, loss of energy, reduced shaving frequency, infertility and loss of muscle strength, were documented.

A general physical and systemic examination was performed. Height and weight were measured, and body mass index was calculated as weight in kilograms divided by height in metres squared. Examination for body-hair distribution, gynaecomastia, testicular abnormalities, muscle wasting and features of chronic liver disease or other endocrine disorders was performed.

Morning venous blood was collected, preferably between 8:00 and 10:00 a.m., for the estimation of free testosterone, LH and FSH. CD4-positive T-lymphocyte count was measured from a blood sample obtained during the same visit or the most recent CD4 count performed within a predefined clinically acceptable interval was recorded from the ART-centre register. Hypogonadism was identified on the basis of reduced testosterone concentration according to the reference range of the institutional laboratory, interpreted along with the participant's clinical features. Participants with reduced testosterone and elevated LH and/or FSH were classified as having primary hypogonadism. Those with reduced testosterone and low or inappropriately normal LH and FSH were classified as having secondary hypogonadism. Participants with hormone values within the laboratory reference ranges were categorized as eugonadal.

CD4 counts were analysed both as a continuous variable and in clinically relevant categories, such as below 200, 200-349, 350-499 and 500 cells/mm³ or above. Gonadal hormone concentrations were correlated with CD4 count, and the prevalence and type of hypogonadism were compared across CD4-count categories.

**Sample Processing**

Approximately 5-7 mL of venous blood was collected from each participant under aseptic precautions. Blood intended for CD4 enumeration was collected in an EDTA anticoagulated tube and transported promptly to the designated laboratory. CD4-positive T-lymphocytes were enumerated by flow cytometry according to the manufacturer's instructions and reported as cells/mm³.

Blood intended for hormone estimation was collected in a plain serum-separator tube. The sample was allowed to clot and was centrifuged at approximately 3,000 revolutions per minute for 10 minutes. The separated serum was analysed immediately or stored at 2-8°C when short-term storage was necessary.

Free testosterone, LH and FSH concentrations were measured using validated immunoassay methods available in the institutional laboratory, with internal quality-control procedures performed according to laboratory protocols. Haemolysed,

lipaemic, improperly labelled or inadequately collected specimens were rejected, and repeat samples were obtained whenever feasible.

**Statistical Methods**

Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics, version 20.0. Continuous variables were examined for normality and summarized as mean with standard deviation or median with interquartile range, as appropriate. Categorical variables were presented as frequencies and percentages with 95% confidence intervals where applicable.

The prevalence of overall, primary and secondary hypogonadism was calculated. Hormone levels between two groups were compared using the independent-samples t test or Mann-Whitney U test. Comparisons across more than two CD4-count categories were performed using one-way analysis of variance or the Kruskal-Wallis test. Associations between categorical variables were assessed using the chi-square test or Fisher's exact test.

Pearson's correlation coefficient was used to evaluate correlations between CD4 count and normally distributed hormone levels; Spearman's rank-correlation coefficient was used for non-normally distributed variables. Multivariable linear or logistic regression analysis was considered to adjust for potential confounders such as age, BMI, duration of HIV infection, ART duration and ART regimen. Effect estimates were reported with 95% confidence intervals. All tests were two-tailed, and a p value <0.05 was considered statistically significant.

**Data Collection**

Information was collected using a predesigned, pretested structured case-record form. The form included sociodemographic details, clinical manifestations of androgen deficiency, anthropometric measurements, duration of HIV infection, ART status and regimen, treatment duration, opportunistic infections, comorbidities, medication history, CD4 count, free testosterone, LH and FSH levels. Each participant was assigned a unique study identification number. Completed forms were checked for accuracy and completeness before data entry. Participant identities and medical information were kept confidential, and study data were used exclusively for research purposes.

## RESULTS

**Table 1. Overall relationship between gonadal status and CD4 count among male HIV patients (N=80)**

| Parameter | n (%) or Mean (SD) | 95% CI | Effect estimate (95% CI) | Test of significance | P value |
|---|---|---|---|---|---|
| Eugonadism | 49 (61.3) | 50.3%-71.2% | Reference | | |
| Any hypogonadism | 31 (38.8) | 28.8%-49.7% | | One-sample proportion z=1.84† | 0.066 |
| Primary hypogonadism | 23 (28.8) | 20.0%-39.5% | | | |
| Secondary hypogonadism | 8 (10.0) | 5.2%-18.5% | | | |
| Overall CD4 count, cells/mm³ | 459 (346) | 382-536 | | | |
| CD4 count in eugonadism | 494 (358) | 391-597 | Reference | | |
| CD4 count in any hypogonadism‡ | 403 (323) | 285-522 | MD=91 cells/mm³ (−62 to 244) | Independent t=1.19 | 0.238 |
| CD4 count across eugonadism, primary and secondary hypogonadism | | | $\eta^2 \approx 0.02$ | One-way ANOVA, F≈0.80 | 0.456 |

†The observed prevalence of hypogonadism was compared with the previously reported prevalence of 29.4% used for sample-size estimation.

‡The combined hypogonadism mean and SD were calculated from the primary and secondary hypogonadism groups.
MD: mean difference; $\eta^2$: eta-squared measure of association.

Table 1 presents the overall relationship between gonadal status and CD4 count among 80 male HIV patients. Of the participants, 49 (61.3%; 95% CI: 50.3%-71.2%) were eugonadal, while 31 (38.8%; 95% CI: 28.8%-49.7%) had hypogonadism. The observed prevalence of hypogonadism was higher than the previously reported prevalence of 29.4% used for sample-size estimation; however, this difference was not statistically significant (z=1.84, p=0.066). Primary hypogonadism was identified in 23 (28.8%; 95% CI: 20.0%-39.5%) participants, whereas secondary hypogonadism was present in 8 (10.0%; 95% CI: 5.2%-18.5%). The overall mean CD4 count was 459 (346) cells/mm³ (95% CI: 382-536).

Eugonadal participants had a higher mean CD4 count of 494 (358) cells/mm³ compared with 403 (323) cells/mm³ among participants with hypogonadism. The mean difference was 91 cells/mm³ (95% CI: −62 to 244), but it was not statistically significant (t=1.19, p=0.238). Similarly, the comparison of CD4 counts across the eugonadal, primary hypogonadism and secondary hypogonadism groups showed no statistically significant difference (F≈0.80, p=0.456). The small effect size ($\eta^2 \approx 0.02$) indicated that gonadal status explained only approximately 2% of the variability in CD4 count.

**Table 2. Serum gonadal hormone levels among adult male HIV patients according to gonadal status (N=80)**

| Hormone | Total (N=80), Mean (SD), 95% CI | Eugonadism (n=49), Mean (SD), 95% CI | Primary hypogonadism (n=23), Mean (SD), 95% CI | Secondary hypogonadism (n=8), Mean (SD), 95% CI | Test of significance | P value |
|---|---|---|---|---|---|---|
| Free testosterone, pg/mL | 7.62 (4.49), 6.62-8.62 | 10.25 (3.68), 9.19-11.31 | 3.37 (1.41), 2.76-3.98 | 3.71 (1.76), 2.24-5.18 | One-way ANOVA, F≈47.18 | <0.001* |
| FSH, mIU/mL | 5.95 (5.23), 4.79-7.11 | 5.39 (4.55), 4.08-6.70 | 8.09 (6.68), 5.20-10.98 | 3.24 (0.93), 2.46-4.02 | One-way ANOVA† | 0.123 |
| LH, mIU/mL | 4.59 (3.00), 3.92-5.26 | 4.91 (3.21), 3.99-5.83 | 4.60 (2.72), 3.42-5.78 | 2.63 (1.50), 1.38-3.88 | One-way ANOVA† | 0.326 |

*Statistically significant at .
†The p values are those reported in the thesis.

Laboratory reference ranges: free testosterone 5.7-30.7 pg/mL; FSH 4.5-22.5 mIU/mL; LH 2.12-10.39 mIU/mL.
Table 2 describes serum free testosterone, FSH and LH levels according to gonadal status. The overall mean free testosterone level was 7.62 (4.49) pg/mL (95% CI: 6.62-8.62). Eugonadal participants had the highest mean free testosterone level at 10.25 (3.68) pg/mL, compared with 3.37 (1.41) pg/mL in primary hypogonadism and 3.71 (1.76) pg/mL in secondary hypogonadism. Free testosterone differed significantly across the three groups (F≈47.18, p<0.001), confirming substantially lower testosterone concentrations in both hypogonadal groups. The overall mean FSH level was 5.95 (5.23) mIU/mL (95% CI: 4.79-7.11). Mean FSH was highest among participants with primary hypogonadism at 8.09 (6.68) mIU/mL, followed by 5.39 (4.55) mIU/mL in the eugonadal group and 3.24 (0.93) mIU/mL in the secondary hypogonadism group. Nevertheless, the overall difference in FSH levels was not statistically significant (p=0.123). The overall mean LH level was 4.59 (3.00) mIU/mL (95% CI: 3.92-5.26). Mean LH was 4.91 (3.21) mIU/mL in eugonadal participants, 4.60 (2.72) mIU/mL in primary hypogonadism and 2.63 (1.50) mIU/mL in secondary hypogonadism. Although LH was lowest in secondary hypogonadism, the difference across the groups was not statistically significant (p=0.326).

**Table 3. Prevalence and type of hypogonadism among male HIV patients (N=80)**

| Gonadal status | n (%) | 95% CI | Effect estimate (95% CI) | Test of significance | P value |
|---|---|---|---|---|---|
| Eugonadism | 49 (61.3) | 50.3%-71.2% | | | |
| Any hypogonadism | 31 (38.8) | 28.8%-49.7% | Prevalence difference from 29.4%=9.4% (−0.6% to 19.4%) | One-sample proportion z=1.84 | 0.066 |
| Primary hypogonadism | 23 (28.8) | 20.0%-39.5% | | | |
| Secondary hypogonadism | 8 (10.0) | 5.2%-18.5% | | | |
| Primary among hypogonadal patients (n=31) | 23 (74.2) | 56.8%-86.3% | Primary-to-secondary ratio=2.88:1 | Exact binomial test‡ | 0.011* |
| Secondary among hypogonadal patients (n=31) | 8 (25.8) | 13.7%-43.2% | Reference | | |

*Statistically significant at 0.05.
‡The exact binomial test compared the proportions of primary and secondary hypogonadism, with 50% as the null expected proportion.

Table 3 presents the prevalence and types of hypogonadism among the study participants. Of the 80 male HIV patients, 49 (61.3%; 95% CI: 50.3%-71.2%) were eugonadal, while 31 (38.8%; 95% CI: 28.8%-49.7%) had hypogonadism. The prevalence of hypogonadism was 9.4 percentage points higher than the previously reported prevalence of 29.4%, although the 95% confidence interval for this difference included zero (−0.6% to 19.4%). Consequently, the difference did not reach statistical significance (z=1.84, p=0.066). In the total study population, primary hypogonadism was present in 23 (28.8%; 95% CI: 20.0%-39.5%) participants, whereas secondary hypogonadism was found in 8 (10.0%; 95% CI: 5.2%-18.5%). Among the 31 hypogonadal participants, 23 (74.2%; 95% CI: 56.8%-86.3%) had primary hypogonadism and 8 (25.8%; 95% CI: 13.7%-43.2%) had secondary hypogonadism. The primary-to-secondary hypogonadism ratio was 2.88:1. An exact binomial test demonstrated that primary hypogonadism was significantly more frequent than secondary hypogonadism (p=0.011).

**Table 4. Association of gonadal hormone levels and hypogonadal status with CD4 count (N=80)**

| Gonadal status | n | CD4 count, Mean (SD), cells/mm³ | 95% CI for mean | Mean difference versus eugonadism (95% CI) | Test of significance | P value |
|---|---|---|---|---|---|---|
| Eugonadism | 49 | 494 (358) | 391-597 | Reference | | |
| Primary hypogonadism | 23 | 388 (289) | 263-513 | −106 (−267 to 55) | Welch t≈−1.34 | 0.186 |
| Secondary hypogonadism | 8 | 447 (432) | 86-808 | −47 (−411 to 317) | Welch t≈−0.31 | 0.762 |
| Any hypogonadism | 31 | 403 (323) | 285-522 | −91 (−244 to 62) | Independent t≈−1.19 | 0.238 |
| Overall comparison across three groups | 80 | | | $\eta^2$≈0.02 | One-way ANOVA, F≈0.80 | 0.456 |

**Gonadal hormone-CD4 analysis**

| Relationship assessed | Statistical measure | 95% CI | Test of significance | P value |
|---|---|---|---|---|
| Free testosterone versus CD4 count | Not estimable from aggregate data | | Pearson/Spearman correlation required | |
| FSH versus CD4 count | Not estimable from aggregate data | | Pearson/Spearman correlation required | |
| LH versus CD4 count | Not estimable from aggregate data | | Pearson/Spearman correlation required | |
| Hypogonadal status versus CD4 count | $\eta^2$≈0.02 | | One-way ANOVA, F≈0.80 | 0.456 |

Table 4 shows the association between gonadal status and CD4 count. The mean CD4 count among the 49 eugonadal participants was 494 (358) cells/mm³ (95% CI: 391-597). Participants with primary hypogonadism had the lowest mean CD4 count at 388 (289) cells/mm³ (95% CI: 263-513), representing a mean reduction of 106 cells/mm³ compared with the eugonadal group. However, the confidence interval for this difference crossed zero (95% CI: −267 to 55), and the difference was not statistically significant (Welch t≈−1.34, p=0.186). Participants with secondary hypogonadism had a mean CD4 count of 447 (432) cells/mm³ (95% CI: 86-808), which was 47 cells/mm³ lower than that of eugonadal participants. This difference was also nonsignificant (95% CI: −411 to 317; Welch t≈−0.31, p=0.762). When primary and secondary hypogonadism were combined, the mean CD4 count was 403 (323) cells/mm³, representing a mean reduction of 91 cells/mm³ compared with the eugonadal group; however, this difference remained statistically nonsignificant (95% CI: −244 to 62; t≈−1.19, p=0.238). The overall comparison across the three gonadal-status groups was likewise nonsignificant (F≈0.80, p=0.456), with a small effect size of $\eta^2$≈0.02. Direct correlations between CD4 count and free testosterone, FSH or LH could not be estimated from the summarized data because paired participant-level measurements were unavailable.

## DISCUSSION

**Table 1: Overall relationship between gonadal status and CD4 count**

In the present study, hypogonadism was identified in 31 of 80 male HIV patients, giving a prevalence of 38.8% (95% CI: 28.8%-49.7%). The remaining 61.3% were eugonadal. This prevalence was close to the 39.1% reported by Dutta et al. (2017)[4] among HIV-infected Indian men, but higher than the 25.9% reported by Bajaj et al. (2017)[5], 23.3% reported by Pongener et al. (2019)[8], and approximately 26% pooled prevalence reported by Santi et al. (2021)[10]. In contrast, Aggarwal et al. (2018)[7] documented a considerably higher prevalence of 66%, possibly because their sample included a larger proportion of patients with advanced immunosuppression and used free testosterone for diagnosis. In ART-naïve Tanzanian men, Iddi et al. (2024)[13] reported a prevalence of 47.9%, which was higher than the present finding. The differences across studies may be attributed to variation in age, disease severity, ART exposure, nutritional status,

testosterone assay, diagnostic cut-off and whether total or free testosterone was used. The present estimate nevertheless lies within the contemporary range of 13%-40% summarized by De Vincentis and Rochira (2023)[12] for men living with HIV.

The overall mean CD4 count was 459 (346) cells/mm³. Eugonadal participants had a higher mean CD4 count than hypogonadal participants 494 (358) versus 403 (323) cells/mm³ with a mean difference of 91 cells/mm³. Although this direction suggested greater gonadal dysfunction with worsening immunological status, the difference was not statistically significant (p=0.238). Similarly, the overall comparison across eugonadal, primary and secondary hypogonadal groups was nonsignificant (p=0.456), with a small effect size ($\eta^2 \approx 0.02$). Pongener et al. (2019)[8] similarly found no significant linear correlation between testosterone and CD4 count, despite observing a significant categorical association between hypogonadism and CD4 strata. By contrast, Bajaj et al. (2017)[5] reported that hypogonadism increased significantly as CD4 count decreased (p=0.002). Aggarwal et al. (2018)[7] also found a significant association between immunodeficiency severity and hypogonadism (p=0.027), with lower free testosterone in patients with CD4 counts below 200 cells/mm³. Dutta et al. (2017)[4] identified CD4 count at HIV diagnosis as a predictor of male hypogonadism. The lack of significance in the present study may reflect the small sample, wide CD4 dispersion, ART-related immune recovery and limited representation of severely immunosuppressed patients.

**Table 2: Gonadal hormone levels according to gonadal status**

The overall mean free testosterone level was 7.62 (4.49) pg/mL. It was substantially higher among eugonadal participants 10.25 (3.68) pg/mL than among patients with primary and secondary hypogonadism, whose mean levels were 3.37 (1.41) and 3.71 (1.76) pg/mL, respectively. The difference was highly significant ($F \approx 47.18$, $p<0.001$). This expected separation supports the biochemical validity of the classification used. Gomes et al. (2016)[2] similarly found a substantial burden of testosterone deficiency among HIV-infected men receiving ART. Slama et al. (2016)[3] demonstrated that free testosterone declined longitudinally with age in both HIV-infected and uninfected men, while men with HIV showed additional effects related to chronic disease and treatment exposure. The meta-analysis by Santi et al. (2021)[10] confirmed that men with HIV had lower free testosterone than HIV-negative controls and emphasized that free testosterone identified more cases than total testosterone. This is particularly relevant because HIV infection may raise sex hormone-binding globulin, resulting in apparently normal total testosterone despite reduced biologically active testosterone. Lachâtre et al. (2022)[11] also demonstrated that hypogonadism remained a relevant comorbidity among young and middle-aged men with virologically suppressed HIV.

The mean FSH level was highest in primary hypogonadism at 8.09 (6.68) mIU/mL, compared with 5.39 (4.55) mIU/mL in eugonadism and 3.24 (0.93) mIU/mL in secondary hypogonadism. Although this pattern was physiologically compatible with greater testicular dysfunction in primary hypogonadism, the overall difference was not statistically significant (p=0.123). Similarly, LH was lowest in secondary hypogonadism 2.63 (1.50) mIU/mL compared with 4.91 (3.21) mIU/mL in eugonadism and 4.60 (2.72) mIU/mL in primary hypogonadism, but the difference was nonsignificant (p=0.326). Aggarwal et al. (2018)[7] likewise found that free testosterone correlated with immunological severity, whereas LH and FSH did not demonstrate significant correlations with CD4 count. Iddi et al. (2024)[13] reported significantly reduced testosterone among newly diagnosed ART-naïve men with HIV, but gonadotropin abnormalities varied according to the level of hypothalamic-pituitary or testicular involvement. Rochira et al. (2015)[1] proposed that low testosterone in HIV frequently represents functional suppression associated with comorbidities, inflammation and frailty rather than irreversible structural gonadal disease. Consequently, free testosterone may be a more sensitive marker of gonadal dysfunction than an isolated LH or FSH measurement.

**Table 3: Prevalence and type of hypogonadism**

Primary hypogonadism was present in 23 participants (28.8% of the total sample), while secondary hypogonadism was found in 8 (10.0%). Among the 31 hypogonadal patients, 74.2% had primary and 25.8% had secondary hypogonadism, producing a primary-to-secondary ratio of 2.88:1. Primary hypogonadism was significantly more frequent than secondary hypogonadism (p=0.011). This finding differs from much of the contemporary literature, in which secondary or hypogonadotropic hypogonadism has generally predominated. Dutta et al. (2017)[4] reported total testosterone below 300 ng/dL in 39.1% of HIV-infected men, but primary hypogonadism was observed in only 7.6%, compared with hypogonadotropic hypogonadism in 31.6%. Similarly, Bajaj et al. (2017)[5] reported secondary hypogonadism in 14 of 21 hypogonadal cases, while Pongener et al. (2019)[8] found that 85.7% of hypogonadal men had secondary hypogonadism. Aggarwal et al. (2018)[7] reported hypogonadotropic hypogonadism in 42% of their total sample. Iddi et al. (2024)[13] also found secondary hypogonadism to be the predominant pattern among ART-naïve men.

Several factors could explain the predominance of primary hypogonadism in the present study. These include differences in gonadotropin thresholds, reliance on a single hormonal measurement, previous opportunistic infections affecting the testes, medication exposure, chronic systemic illness and small numbers in the secondary group. Furthermore, an LH level

within the population reference interval may be physiologically inappropriate in the presence of markedly reduced testosterone and may therefore indicate secondary rather than primary dysfunction. Wong et al. (2017)[6] and De Vincentis and Rochira (2023)[12] emphasized that the interpretation of gonadotropins in HIV is complex because functional hypothalamic-pituitary suppression, altered sex hormone-binding globulin and systemic illness can lead to mixed or borderline biochemical patterns. Repeated morning hormone measurements and concurrent assessment of total testosterone, SHBG, calculated free testosterone and prolactin would improve etiological classification.

**Table 4: Gonadal status and CD4 count**

Participants with primary hypogonadism had the lowest mean CD4 count at 388 (289) cells/mm³, compared with 494 (358) cells/mm³ in eugonadal participants. The mean difference was −106 cells/mm³, but its confidence interval was wide and included zero (95% CI: −267 to 55; p=0.186). The secondary hypogonadism group had a mean CD4 count of 447 (432) cells/mm³, which was 47 cells/mm³ lower than the eugonadal group but was also nonsignificant (p=0.762). When both types of hypogonadism were combined, the mean CD4 count remained 91 cells/mm³ lower than in eugonadal participants, although this difference did not reach statistical significance (p=0.238). Thus, the findings indicated a tendency toward lower CD4 counts among hypogonadal men, particularly those with primary hypogonadism, but the evidence was insufficient to establish an independent association.

The present nonsignificant association agrees partly with Pongener et al. (2019)[8], who found no significant Pearson correlation between testosterone and CD4 count. It contrasts with Aggarwal et al. (2018)[7], who demonstrated progressively lower free testosterone and a higher prevalence of hypogonadism with declining CD4 count. Bajaj et al. (2017)[5] similarly found a significant association between hypogonadism and reduced CD4 count. Dutta et al. (2017)[4] reported that CD4 count at diagnosis predicted subsequent male hypogonadism, suggesting that past severe immunosuppression or nadir CD4 count may be more informative than a single current CD4 measurement. In virologically suppressed cohorts, Lachâtre et al. (2022)[11] observed persistent hypogonadism despite effective ART, indicating that endocrine dysfunction may continue after immunological recovery. Rochira et al. (2015)[1] also related reduced testosterone more strongly to multimorbidity and poor overall health than to HIV markers alone.

## CONCLUSION

Hypogonadism was a common endocrine abnormality among male patients living with HIV, affecting 38.8% of the study population. Primary hypogonadism was the predominant type, accounting for 74.2% of hypogonadal cases, and was significantly more frequent than secondary hypogonadism. Free testosterone levels differed significantly across gonadal-status groups and were markedly lower in both primary and secondary hypogonadism than in eugonadal participants. Although FSH was highest in primary hypogonadism and LH was lowest in secondary hypogonadism, these differences were not statistically significant. Hypogonadal participants had a lower mean CD4 count than eugonadal participants; however, neither the pairwise differences nor the overall association between gonadal status and CD4 count reached statistical significance. The small effect size indicated that current CD4 count explained little of the variation in gonadal status. These findings suggest that hypogonadism in men living with HIV is multifactorial and may not be determined by current immunological status alone. Routine clinical assessment for symptoms of androgen deficiency, supported by appropriately timed hormonal evaluation, may facilitate early diagnosis and management. Larger prospective studies using repeated morning hormone measurements and participant-level multivariable analyses are required to clarify the relationship between gonadal hormones, nadir and current CD4 counts, ART exposure and HIV disease severity.

## LIMITATIONS OF STUDY

1. The study was conducted at a single tertiary-care centre, limiting the generalizability of its findings to other populations and healthcare settings.
2. The relatively small sample size, particularly the eight participants with secondary hypogonadism, reduced statistical power and produced wide confidence intervals.
3. The cross-sectional design did not establish a temporal or causal relationship between immunological status and the development of hypogonadism.
4. Gonadal hormones were assessed at a single point in time. Testosterone levels may exhibit biological and diurnal variation, and repeat morning measurements would have improved diagnostic reliability.
5. The study relied principally on free testosterone, LH and FSH. Simultaneous assessment of total testosterone, sex hormone-binding globulin, albumin, prolactin and estradiol would have allowed more comprehensive classification.
6. Direct Pearson or Spearman correlations between individual hormone levels and CD4 count could not be estimated from the aggregate data used for analysis.
7. Current CD4 count may not adequately represent the cumulative severity of HIV infection. Nadir CD4 count and longitudinal changes in CD4 count were not evaluated.
8. Potential confounding variables, including age, BMI, nutritional status, smoking, alcohol consumption, opportunistic infections, comorbidities and medication use, may have influenced hormone concentrations.

9. The effects of ART duration, adherence, treatment regimen and viral suppression were not comprehensively adjusted through multivariable analysis.
10. Classification into primary and secondary hypogonadism may have been affected by the small groups, laboratory reference ranges and the absence of repeated gonadotropin measurements.
11. HIV-negative age-matched controls were not included; therefore, the magnitude of gonadal dysfunction attributable specifically to HIV infection could not be determined.
12. Clinical symptoms of androgen deficiency and their relationship with biochemical hypogonadism were not evaluated using a standardized validated instrument.

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