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Beyond Viral Load: The Clinical and Endocrine Profile of ART-Naive HIV-Infected Men with Hypogonadism, Opportunistic Infections, and Malnutrition

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A B S T R A C T

In patients with advanced human immunodeficiency virus (HIV), the clinical presentation often extends beyond immunodeficiency to a syndemic of interacting comorbidities. Male hypogonadism is a critical but often under-recognized endocrine dimension of this syndrome. This study aimed to characterize the clinical, metabolic, and endocrine profile of antiretroviral therapy (ART)-naive men to provide a comprehensive baseline understanding of this syndemic state before therapeutic intervention. An analytical cross-sectional study was conducted from April to October 2024, enrolling 64 consecutively presenting ART-naive men with HIV at a tertiary hospital in Palembang, Indonesia. We performed a comprehensive assessment including WHO clinical staging, nutritional evaluation (BMI), and screening for comorbidities. Endocrine status was assessed by measuring total testosterone, Luteinizing Hormone (LH), and serum albumin, from which bioavailable testosterone was calculated using the Vermeulen formula. Bivariate correlations and comparative analyses were conducted to explore relationships between variables. The cohort presented with profound immunodeficiency (median CD4 count: 23.5 cells/μL) and advanced disease (92.2% in WHO Stage 3 or 4). A high burden of opportunistic infections (40.6% pulmonary tuberculosis) and malnutrition (48.4% underweight; median serum albumin: 3.25 g/dL) was observed. Based on total testosterone (<300 ng/dL), the prevalence of hypogonadism was 32.8%. However, analysis using the more physiologically relevant calculated bioavailable testosterone (<70 ng/dL) revealed a higher prevalence of 42.2%. Secondary (hypogonadotropic) hypogonadism was the overwhelmingly dominant etiology (28.1%). Bioavailable testosterone was significantly and positively correlated with both CD4 count (ρ=0.35, p=0.005) and BMI (ρ=0.41, p=0.001). In conclusion, ART-naive men presenting with advanced HIV in this setting are caught in a syndemic of immunodeficiency, infectious disease, malnutrition, and profound endocrine dysfunction. The high prevalence of secondary hypogonadism, strongly associated with the severity of immune collapse and poor nutritional status, highlights the HPG axis as a key casualty of systemic illness. These findings provide a compelling rationale for integrating routine hormonal and metabolic screening into the initial assessment of all men newly diagnosed with HIV.

1. Introduction

The human immunodeficiency virus (HIV) pandemic, despite monumental advances in antiretroviral therapy (ART), continues to pose a profound challenge to global health.[1] While ART has transformed HIV into a manageable chronic condition for millions, the clinical reality, particularly in resource-limited settings, is often defined by late presentation.[2] In these contexts, clinicians are confronted not with a simple viral infection, but with

the advanced sequelae of years of unchecked viral replication: Acquired Immune Deficiency Syndrome (AIDS). The paradigm of HIV care must therefore extend "beyond viral load" to address the complex web of pathologies that constitute the advanced disease state. A powerful framework for understanding this complexity is the syndemic model, which posits that diseases and health conditions can cluster and interact synergistically within a population, exacerbating the prognosis for each. In the context of advanced HIV, a well-recognized and devastating syndemic exists between the virus, malnutrition, and opportunistic infections (OIs), particularly tuberculosis (TB).[3] Uncontrolled HIV replication destroys the immune system, creating a state of profound vulnerability to OIs like TB. The active OI, in turn, fuels a catabolic and inflammatory state that drives malnutrition and wasting. This malnutrition further cripples the already compromised immune system, creating a vicious cycle of accelerating disease progression and mortality.[4]

Within this established syndemic, the endocrine system, a critical regulator of metabolism, immunity, and homeostasis, is a major but often overlooked casualty. Male hypogonadism, a state of testosterone deficiency, is one of the most common and clinically significant endocrinopathies in men with HIV.[5] This is not merely a consequence of aging or lifestyle, but a direct result of the systemic illness itself, a condition more accurately termed "sickness-induced hypogonadism" or a manifestation of non-gonadal illness syndrome (NGIS).[6] The pathophysiology is predominantly central, originating from the disruption of the hypothalamic-pituitary-gonadal (HPG) axis.[7] The intense, chronic inflammatory state driven by HIV and co-infections, mediated by cytokines like TNF-α and IL-6, suppresses the central hormonal cascade, leading to secondary (hypogonadotropic) hypogonadism. The clinical consequences of this endocrine failure are severe and contribute directly to the syndemic's cycle.[8] Testosterone deficiency exacerbates muscle wasting (sarcopenia), decreases bone density, and is strongly linked to fatigue, depression, cognitive impairment, and diminished quality of life—symptoms that are often mistakenly attributed solely to HIV or its complications.[9] Despite this understanding, a critical knowledge gap persists regarding the precise characteristics of this endocrine dysfunction at the crucial moment of initial HIV diagnosis, before the confounding metabolic and hormonal effects of ART are introduced.[10] This is particularly true in Southeast Asian populations. Therefore, this study was designed within the conceptual framework of the syndemic model. It sought to answer several key research questions in a cohort of ART-naive men with advanced HIV: 1) What is the prevalence and, critically, the etiological type (primary vs. secondary) of hypogonadism, when assessed using both total and the more physiologically accurate bioavailable testosterone? 2) To what extent are the core components of the syndemic—severe immunodeficiency (CD4 count) and malnutrition (BMI)—associated with testosterone levels? 3) What is the full constellation of clinical comorbidities and patient-reported symptoms that define the endocrine dimension of this pre-treatment syndemic state?

The novelty of this study lies in its focused, multi-dimensional characterization of this specific syndemic in an ART-naive Southeast Asian cohort, moving beyond simple prevalence reporting to explore the statistical and physiological links between its components. The primary aim was to provide a comprehensive baseline of the immunological, nutritional, infectious, and endocrine pathologies present at diagnosis. We hypothesized that secondary hypogonadism would be highly prevalent and that its severity would be directly correlated with the severity of immunodeficiency and malnutrition. By elucidating these connections, this research seeks to build a robust, evidence-based case for the integration of hormonal and metabolic screening into the standard initial assessment of all men newly diagnosed with HIV, facilitating earlier, more holistic interventions to improve long-term health outcomes.

2. Methods

This investigation was conducted as an analytical observational study with a cross-sectional design. The study was carried out between April 2024 and October 2024 at the inpatient and outpatient units of Mohammad Hoesin General Hospital, a national tertiary referral and teaching hospital in Palembang, South Sumatra, Indonesia. The study protocol received full ethical approval from the Institutional Review Board of the Faculty of Medicine, Universitas Sriwijaya. The study population comprised adult male patients newly diagnosed with HIV who had not yet initiated ART. A consecutive sampling strategy was employed, wherein every male patient meeting the eligibility criteria during the study period was invited to participate to minimize selection bias. Of 86 individuals initially screened, 22 were excluded (15 due to incomplete laboratory data preventing calculation of key variables, 7 due to hemolyzed samples unsuitable for hormonal analysis). The final cohort consisted of 64 participants who provided written informed consent and completed all study procedures. Inclusion criteria: (1) Adult male aged 18 years or older; (2) Confirmed HIV infection as per Indonesian national guidelines (three reactive rapid antibody tests); (3) Antiretroviral-naive status. Exclusion criteria: (1) Known pre-existing causes of hypogonadism (such as Klinefelter syndrome, history of orchiectomy, diagnosed pituitary tumors); (2) Current or recent (within 3 months) use of medications known to significantly alter HPG axis function, including systemic corticosteroids, opioids, or anabolic steroids; (3) Use of medications known to be potent inhibitors of steroidogenesis (such as ketoconazole) at the time of blood sampling; (4) Inability to provide informed consent. A standardized case report form was used to collect data through direct patient interviews, comprehensive clinical examinations, and review of medical records.

This included age, educational attainment, occupation, and self-reported HIV transmission risk factors. Clinical stage of HIV was classified according to the 2007 WHO staging system. Nutritional status was evaluated by calculating Body Mass Index (BMI) in kg/m^2. Morning (08:00-10:00) venous blood samples were collected after an overnight fast. All assays were performed at the hospital's accredited central laboratory. Absolute $CD4^+$ T-lymphocyte counts were measured by flow cytometry (BD FACSCount™). Total serum testosterone and luteinizing hormone (LH) were measured by chemiluminescent immunoassay (CLIA). Serum albumin was measured using the bromocresol green method. A comprehensive panel included a complete blood count, renal function tests (urea, creatinine), liver function tests (AST, ALT), and a full lipid profile (total cholesterol, HDL, LDL, triglycerides). Three validated Indonesian-language questionnaires were administered: Pittsburgh Sleep Quality Index (PSQI): To assess sleep quality over the past month; Hamilton Depression Rating Scale (HAM-D): To screen for and rate the severity of depressive symptoms; International Index of Erectile Function (IIEF-5): To assess erectile function. Nutritional Status: Defined by BMI as Underweight (<18.5 kg/m^2), Normal weight (18.5–22.9 kg/m^2), or Overweight (≥23.0 kg/m^2) based on Asia-Pacific criteria. Dyslipidemia: Defined according to NCEP ATP III guidelines as the presence of one or more of the following: Total Cholesterol ≥200 mg/dL, LDL Cholesterol ≥130 mg/dL, HDL Cholesterol <40 mg/dL, or Triglycerides ≥150 mg/dL. Anemia: Defined according to WHO criteria as Hemoglobin <13.0 g/dL. Questionnaire Scoring: PSQI: A global score >5 was defined as "Poor Sleep Quality." HAM-D: Scores were categorized as Normal (0-7), Mild Depression (8-16), Moderate Depression (17-23), or Severe Depression (>23). IIEF-5: Scores were categorized as Normal (22-25), Mild Dysfunction (17-21), Mild-to-Moderate (12-16), Moderate (8-11), or Severe (<8). Hypogonadism Definition and Classification: The laboratory reference range for serum LH was 1.7–8.6 IU/L; Biochemical Hypogonadism (Total T): Defined as a total morning testosterone level <300 ng/dL; Biochemical Hypogonadism (Bioavailable T): Defined as a calculated bioavailable testosterone level <70 ng/dL; Primary Hypogonadism: Low total testosterone (<300

ng/dL) with a compensatory high serum LH (>8.6 IU/L); Secondary Hypogonadism: Low total testosterone (<300 ng/dL) with a non-compensatory, "inappropriately normal" or low serum LH (≤8.6 IU/L); Calculation of Bioavailable Testosterone: To provide a more physiologically accurate assessment of androgen status in this cohort with low albumin, bioavailable testosterone was calculated for each participant using the validated Vermeulen formula, which uses total testosterone, albumin, and a fixed value for SHBG (as direct measurement was unavailable).

Data were analyzed using SPSS version 25.0. Data distribution normality was assessed with the Kolmogorov-Smirnov test. Normally distributed continuous data were presented as mean ± standard deviation (SD), while non-normally distributed data were presented as median and interquartile range (IQR) or minimum-maximum values. Categorical data were presented as frequencies and percentages. To explore relationships between key variables, non-parametric Spearman's rank correlation coefficient (ρ) was used. To compare groups (hypogonadal vs. eugonadal), the Mann-Whitney U test was used for non-normally distributed continuous variables. A p-value of <0.05 was considered statistically significant for all inferential tests.

3. Results and Discussion

Figure 1 correctly identifies the central driving force of the entire pathology. The figure quantifies this collapse with stark precision, noting a median $CD4^+$ T-lymphocyte count of a critically low 23.5 cells/μL. This value is profoundly significant; a healthy individual typically has a CD4 count ranging from 500 to 1,500 cells/μL. A count below 200 cells/μL is the defining threshold for acquired immune deficiency syndrome (AIDS), placing the individual at high risk for serious illness. A median of 23.5 cells/μL signifies that the typical patient represented here is not just immunocompromised but is in a state of near-total failure of cell-mediated immunity, far beyond the initial AIDS diagnostic threshold. This immunological devastation is clinically manifested by the fact that 92.2% of these individuals present with Advanced Disease, classified as WHO Stage 3 or 4. This indicates that they are not seeking care due to the HIV diagnosis itself but because of the severe, life-threatening illnesses that have developed as a direct consequence of their collapsed immune systems. This initial stage, as depicted in Figure 1, is not merely one component among many; it is the foundational event from which all subsequent pathologies emanate. The catastrophic failure of the immune system triggers a triad of immediate, interconnected consequences. The first is a state of systemic inflammation & cytokine storm. Unchecked HIV replication and the presence of co-infections like tuberculosis (TB) create a chronic state of immune activation. The body is flooded with pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), Interleukin-1 (IL-1), and Interleukin-6 (IL-6). This is not a healthy, controlled inflammatory response but a dysregulated, persistent "storm" that becomes profoundly catabolic and damaging to the host's own tissues. This inflammatory state and the lack of immune surveillance directly lead to the second consequence, opportunistic infections (OIs). Figure 1 highlights the most prevalent OIs in this population, with Pulmonary Tuberculosis affecting a staggering 40.6% of individuals, followed by Oral Candidiasis (37.5%) and Pneumocystis Pneumonia (15.6%). These are not random infections; they are classic AIDS-defining illnesses that thrive in the absence of a functional T-cell response. Each OI adds its own inflammatory burden and metabolic demand, further fueling the cytokine storm and pushing the patient deeper into a state of critical illness. The third consequence, inextricably linked to the first two, is malnutrition & wasting. The chronic inflammatory state is inherently catabolic, promoting the breakdown of muscle and fat tissue. This is compounded by the symptoms of the OIs themselves, such as the difficulty swallowing associated with oral candidiasis or the anorexia and increased metabolic rate caused by TB. Figure 1 quantifies this with a finding of 48.4% of individuals being underweight (BMI < 18.5) and a low median serum albumin of 3.25 g/dL, a robust marker

of both malnutrition and inflammation. The high prevalence of anemia (85.9%) is also a feature of this chronic inflammatory state, driven by cytokine-mediated disruption of iron metabolism. The final level of the cascade illustrates how the preceding syndemic of inflammation, infection, and wasting leads to a comprehensive failure of other bodily systems. The figure highlights an endocrine collapse, specifically secondary hypogonadism. The prevalence of this condition, based on the more accurate measure of bioavailable testosterone, is a high 42.2%. Crucially, Figure 1 shows that this is not a random occurrence but is statistically correlated with the core drivers of the syndemic; it is correlated with both low CD4 count ($p=0.005$) and low BMI ($p=0.001$). This demonstrates that the endocrine failure is a direct consequence of the severity of the immunodeficiency and wasting, as the inflammatory cytokines and metabolic stress suppress the brain's ability to signal for testosterone production. Concurrently, a profound Metabolic Derangement occurs. The figure notes that 81.3% of individuals suffer from inflammatory dyslipidemia, characterized by low protective HDL cholesterol and high triglycerides. This is not a diet-related lipid issue but a metabolic signature of the chronic cytokine storm, which actively reprograms liver lipid metabolism, increasing long-term cardiovascular risk. Ultimately, this entire cascade of physiological failure culminates in a Collapsed Quality of Life. The objective data from validated questionnaires show the human impact of this syndemic. An overwhelming 81.0% of individuals report poor sleep quality, likely a result of night sweats from TB, the neuropsychiatric effects of inflammation, and hormonal imbalance. A significant portion suffers from mild depression (38.1%) and erectile dysfunction (32.8%), both complex symptoms driven by the interplay of low testosterone, psychological distress, and systemic illness. Figure 1 masterfully narrates a story of progressive, interconnected failure. It illustrates that in an ART-naive patient with advanced disease, a low CD4 count is not just a lab value but the trigger for a devastating cascade that leads to opportunistic infections, systemic inflammation, profound wasting, and ultimately, the collapse of endocrine, metabolic, and personal well-being.

Figure 2 presents two distinct values, highlighting a crucial scientific and clinical distinction. Based on the standard measurement of total testosterone, 32.8% of individuals were found to be hypogonadal. However, the figure reveals a significantly higher and more physiologically accurate prevalence of 42.2% when using calculated bioavailable testosterone. This difference is not a trivial statistical variation; it is central to understanding the true state of androgen deficiency in these patients. Total testosterone measures all testosterone in the bloodstream, including the large portion that is tightly bound to transport proteins like sex hormone-binding globulin (SHBG) and albumin. In healthy individuals, this provides a reasonable proxy for hormonal status. However, in patients with severe chronic inflammatory and malnourished states, such as those in this study, the liver's production of these binding proteins is often suppressed. With lower levels of binding proteins, the total testosterone level can be misleadingly low, even if the amount of "active" testosterone is adequate. Conversely, and more importantly, bioavailable testosterone represents the fraction of the hormone that is not tightly bound to SHBG and is therefore free to enter cells and exert its biological effects on muscle, bone, brain, and other tissues. By calculating this value, one gets a much clearer picture of the body's true exposure to functional androgens. The finding that 42.2% of the cohort is deficient in this active fraction reveals that the problem is even more widespread than conventional testing would suggest. This underscores the inadequacy of relying on total testosterone alone in this specific clinical context and makes a powerful case for using more nuanced assessments to unmask the true prevalence of this debilitating condition. An astonishing 85.7% of the hypogonadal cases were classified as secondary (central) hypogonadism, while only a small minority, 14.3%, were due to primary (testicular) hypogonadism.

Figure 1. The cascade of failure in advanced, untreated HIV.

This finding is paramount to the pathophysiological narrative. Primary hypogonadism signifies a failure of the testes themselves; they are damaged and unable to produce testosterone despite receiving the proper signals from the brain. Secondary hypogonadism, in contrast, signifies a failure of the brain's central command centers—the hypothalamus and pituitary gland. In this state, the testes are capable of functioning, but they are not receiving the necessary hormonal signal (Luteinizing Hormone, or LH) to do their job. The overwhelming dominance of the secondary form, as shown in Figure 2, confirms that the low testosterone seen in these patients is not primarily caused by direct viral or infectious damage to the testes. Instead, it is a consequence of the systemic illness suppressing the brain. The chronic inflammation and severe metabolic stress of the HIV syndemic effectively send powerful inhibitory signals to the hypothalamus and pituitary, shutting down the reproductive axis as an adaptive—or maladaptive—

survival response. This confirms the model of "sickness-induced hypogonadism," where the endocrine system becomes a casualty of systemic chaos. The final component of Figure 2 provides the statistical evidence that links this endocrine failure directly to the core components of the syndemic: immune collapse and malnutrition. The figure presents two highly significant correlations. First, it reveals a significant positive correlation between bioavailable testosterone and the severity of immune collapse, with a p-value of 0.005. A p-value this small indicates that the observed relationship is highly unlikely to be due to random chance. It provides robust statistical evidence that as a patient's $CD4^+$ T-cell count falls, their level of active testosterone tends to fall in a related manner. This quantitatively tethers the failure of the endocrine system to the failure of the immune system. Second, Figure 2 shows an even stronger link to malnutrition, with a p-value of 0.001 for the correlation with body mass index (BMI). This extremely low p-value signifies a very strong statistical connection. It demonstrates that patients with lower BMI—a proxy for wasting and malnutrition—also have significantly lower levels of bioavailable testosterone. This supports the physiological model wherein the body, sensing a state of severe energy deficit, actively downregulates the energetically expensive reproductive axis to conserve resources. Figure 2 tells a complete and compelling story. It demonstrates that testosterone deficiency is not only highly prevalent in this population (affecting over 40%) but that its root cause is a central failure of the brain's hormonal signaling, driven by the systemic stress of the disease. Most importantly, it provides the statistical proof that this endocrine casualty is not an isolated event but is intimately and significantly intertwined with the two pillars of the advanced HIV syndemic: the collapse of the immune system and the wasting of the body.

The strongest and most significant relationship identified is between bioavailable testosterone and BMI, with a correlation coefficient of $\rho = 0.41$. The associated p-value of 0.001 is highly significant, indicating that this strong positive correlation is extremely unlikely to be a result of random chance. This finding provides robust statistical proof for the physiological link between nutritional status and the endocrine system. It demonstrates that as a patient's body mass index declines, a clear and measurable decline in their active testosterone levels occurs in parallel. This supports the biological model where the body, in a state of severe energy deficit and wasting, actively downregulates the metabolically costly reproductive axis to conserve resources for survival. A similarly significant finding is the correlation between Bioavailable Testosterone and CD4 Count, which yielded a coefficient of $\rho = 0.35$. The p-value of 0.005 confirms that this is a statistically significant relationship, linking the failure of the endocrine system directly to the failure of the immune system. As the patient's immune defenses collapse (reflected by a falling CD4 count), their hormonal system responsible for androgen production also deteriorates. This suggests a shared underlying driver, likely the systemic inflammation and cytokine storm characteristic of advanced, uncontrolled HIV, which negatively impacts both immune cell survival and central hormonal signaling. Figure 3 shows a non-significant trend between Bioavailable Testosterone and Serum Albumin ($\rho = 0.21$, $p=0.098$). While this relationship did not meet the threshold for statistical significance, the positive trend suggests a potential link between androgen status and this dual marker of inflammation and malnutrition, warranting further investigation in larger cohorts. Figure 3 provides a stark visual comparison between patients who remained eugonadal (normal testosterone) and those who became hypogonadal. This analysis reinforces the findings of the correlation analysis by demonstrating clear, statistically significant differences in the clinical status of these two groups. When examining the Median $CD4^+$ T-Cell Count, a dramatic difference emerges. The eugonadal group had a median CD4 count of 44.5 cells/μL, whereas the hypogonadal group had a median count of only 16.0 cells/μL. This nearly threefold difference is highly statistically significant ($p = 0.011$) and provides powerful evidence

that patients with more severe immunodeficiency are far more likely to suffer from hypogonadism. A similar pattern is observed in the Median Body Mass Index (BMI). The eugonadal patients had a median BMI of 20.4 kg/m², which is in the low-normal range. In stark contrast, the hypogonadal patients had a median BMI of 17.9 kg/m², a value that falls squarely in the underweight category. This difference is also highly statistically significant ($p = 0.002$), confirming that patients with poorer nutritional status and more advanced wasting are significantly more likely to be androgen deficient. Figure 3 uses rigorous statistical methods to dissect the syndemic. It does not just state that problems co-exist; it demonstrates that they are mathematically linked. The correlation analysis reveals that as immunity and nutrition decline, so does testosterone. The group comparison analysis confirms this by showing that the subgroup of patients who develop hypogonadism are, in fact, the very same patients who are more immunodeficient and more malnourished. This provides a powerful, data-driven argument that endocrine failure in advanced HIV is not an isolated event but a direct and measurable consequence of the broader systemic collapse.

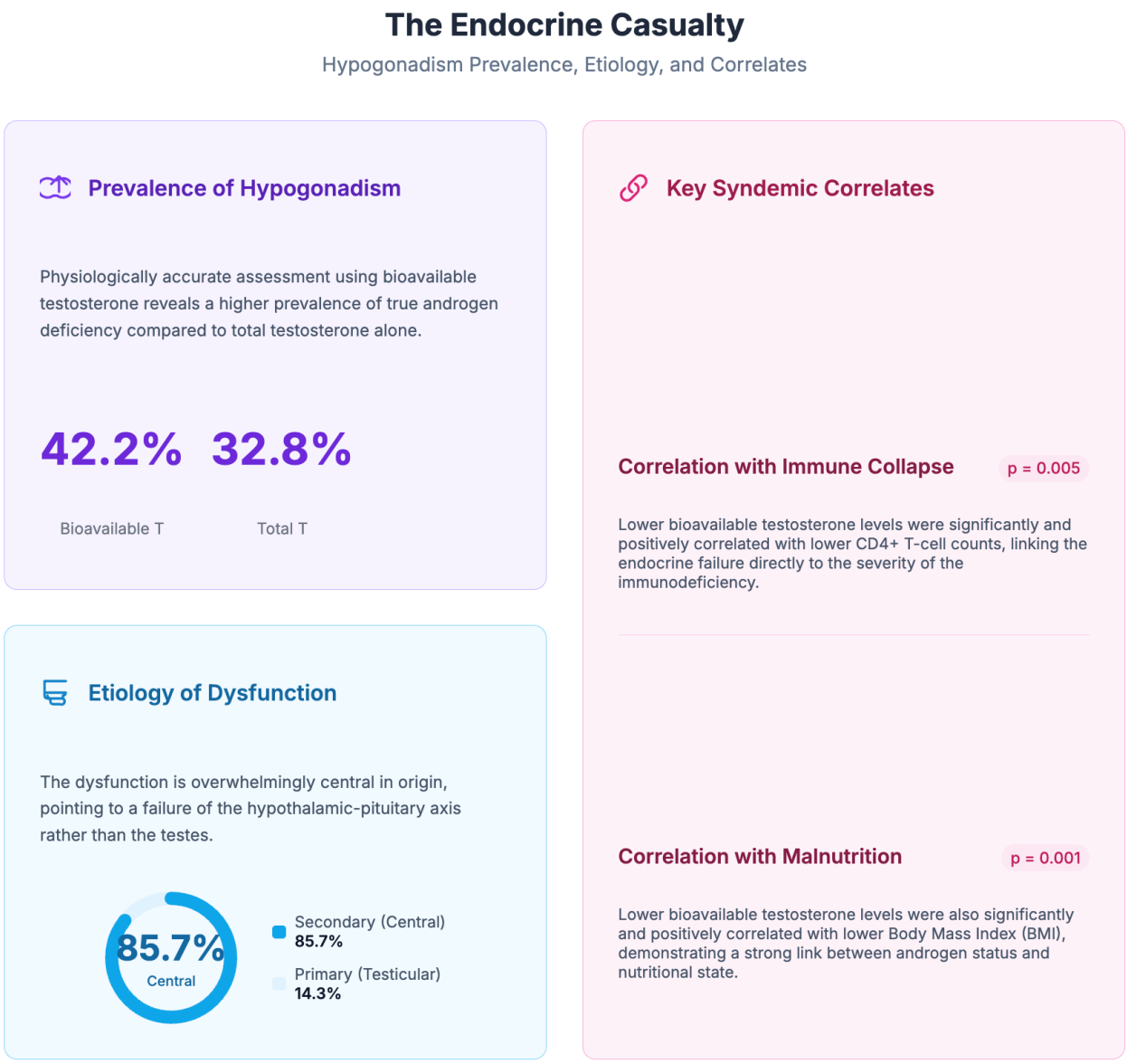

Figure 2. The endocrine casualty.

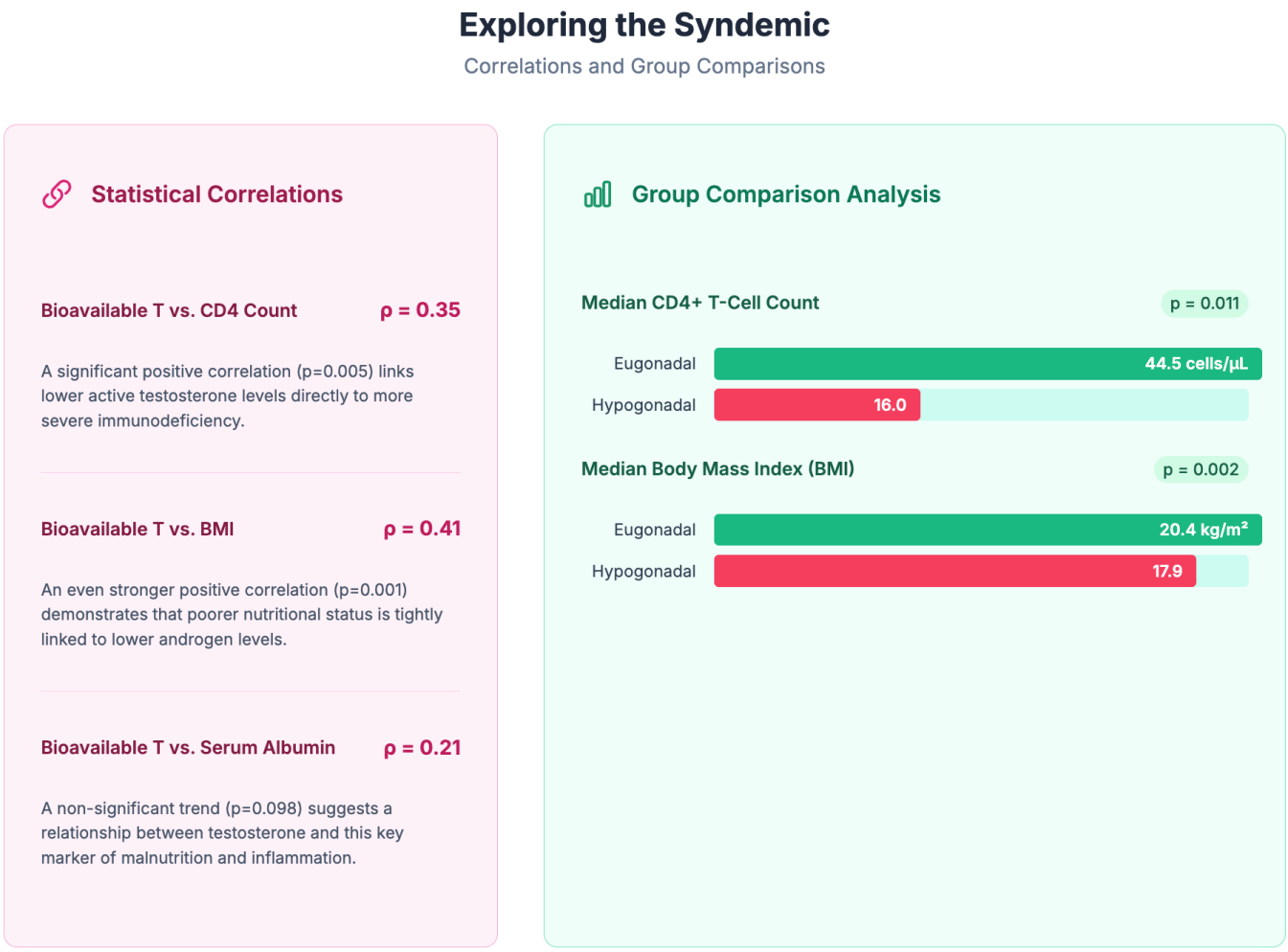

Figure 3. Exploring the syndemic.

The most pervasive issue highlighted in Figure 4 is the near-universal prevalence of Poor Sleep Quality, affecting a staggering 81.0% of the individuals in this cohort. This finding suggests that for these patients, the basic human need for restful sleep has been almost entirely eroded. The figure astutely describes this not as a single problem but as a "final common pathway" for multiple syndemic insults. First, the physical symptoms of opportunistic infections, such as the drenching night sweats characteristic of tuberculosis, physically disrupt sleep architecture, forcing awakenings and preventing sustained rest. Second, there are the direct neuropsychiatric effects of systemic cytokines. Pro-inflammatory molecules like TNF-α and IL-6 are known to cross the blood-brain barrier and interfere with the central nervous system's regulation of sleep, promoting a state of light, fragmented, and unrefreshing sleep while suppressing the deep, restorative slow-wave stages. Finally, the immense psychological weight of receiving a life-altering diagnosis contributes to a state of hyperarousal and anxiety, making it difficult to initiate and maintain sleep. This collapse of sleep is more than just a symptom; it becomes a driver of further decline, exacerbating the fatigue, cognitive impairment, and mood disturbances that plague these patients. Figure 4 quantifies the significant emotional and psychological burden, noting that 38.1% of patients experienced Mild Depression. The figure's description correctly identifies a dual-driver model for this mental

health crisis. On one hand, there is the undeniable immense psychological burden of the diagnosis itself, encompassing fear, social stigma, and uncertainty about the future. On the other hand, and equally important, are the direct biological effects of inflammation on brain chemistry. Chronic inflammation, as seen in this cohort, can alter neurotransmitter pathways. For instance, it is known to divert the metabolism of the amino acid tryptophan. Instead of being converted into serotonin (a key neurotransmitter for mood regulation), it is shunted down the kynurenine pathway, producing metabolites that can be neurotoxic and directly contribute to depressive symptoms. This insight is critical because it reframes the depression seen in these patients not merely as a psychological reaction but as a direct neurobiological consequence of their underlying physical illness. Figure 4 addresses a deeply personal and often overlooked consequence of the disease: Erectile Dysfunction, which affected 32.8% of the cohort. The figure explains this as a multifactorial issue, a convergence of hormonal, psychological, and vascular problems. The central loss of libido due to low testosterone is a direct link to the endocrine casualty detailed previously. Without adequate androgen levels, the central drive for sexual activity is diminished. This is compounded by the psychological distress of depression and anxiety, which further suppress libido and performance confidence. Perhaps most physiologically direct are the vascular effects of inflammatory dyslipidemia. The chronic inflammation damages the delicate lining of blood vessels (the endothelium), impairing their ability to produce nitric oxide—the key molecule responsible for the vasodilation required to achieve and maintain an erection.

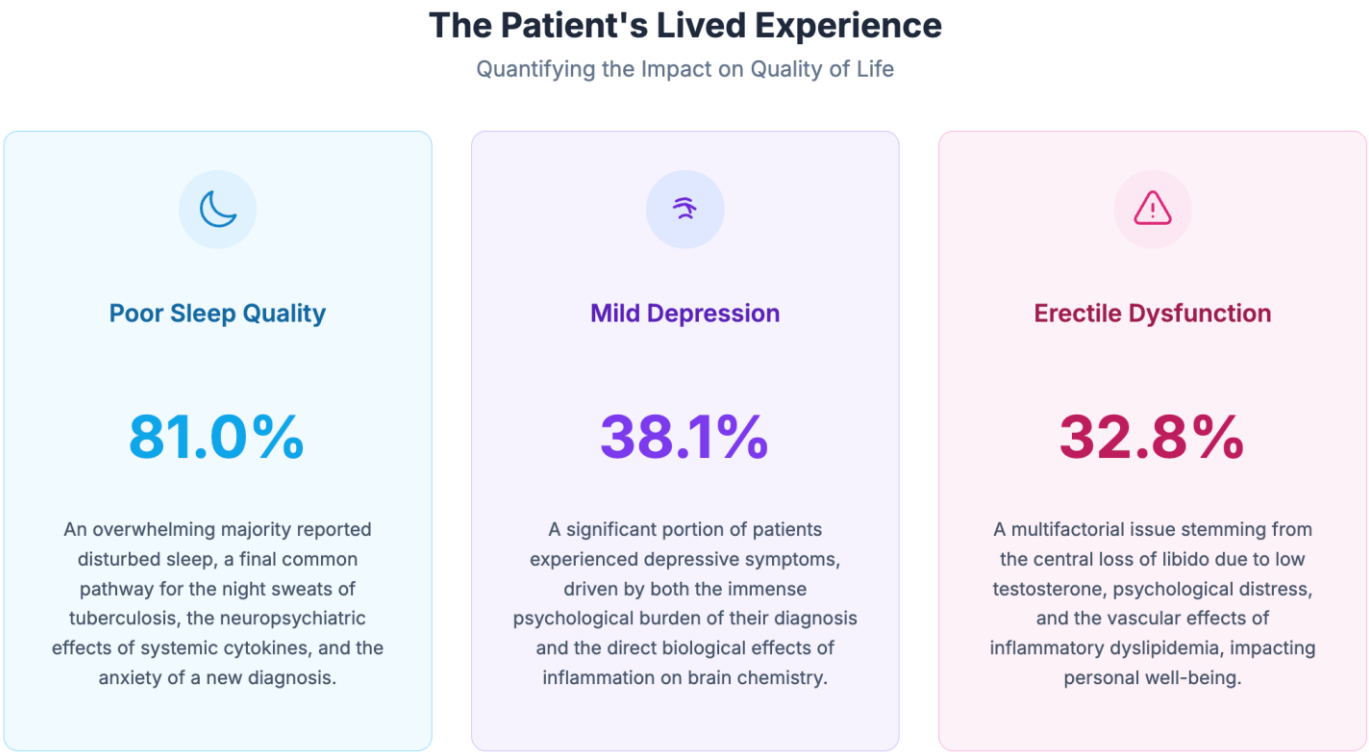

Figure 4. The patient's lived experience.

This study provides a multi-dimensional, in-depth analysis of the clinical state of ART-naive men at the point of HIV diagnosis in a resource-limited Indonesian setting.[11] By framing our investigation within the syndemic model, our findings move beyond a simple description of comorbidities to illuminate the profound and synergistic interactions between immune collapse, infectious disease, malnutrition, and endocrine failure. The data paint a stark picture of a patient population caught in a vicious cycle of systemic decline, arguing compellingly for a clinical approach that looks far beyond viral load. The foundational finding of this study is the state of near-complete immune collapse, evidenced by a median CD4 count of 23.5 cells/μL.[12] This is the engine driving the entire syndemic. Such a low value signifies years of unchecked viral replication, leading to massive depletion of helper T-cells and a state of profound vulnerability. This vulnerability was realized in our cohort through the high prevalence of opportunistic infections, with pulmonary tuberculosis (40.6%) being the most formidable co-pathogen. The co-existence of uncontrolled HIV and active TB creates a perfect storm of systemic inflammation. The host immune system, particularly macrophages and dendritic cells, recognizes pathogen-associated molecular patterns (PAMPs) on both the HIV virion and *Mycobacterium tuberculosis*.[13] This recognition, mediated by Toll-like receptors (TLRs), triggers a massive and sustained release of pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Furthermore, HIV-induced damage to the gut mucosal barrier leads to the translocation of microbial products, such as lipopolysaccharide (LPS), from the gut lumen into the systemic circulation. This LPS acts as another powerful PAMP, constantly re-stimulating the inflammatory cascade.[14] In parallel, widespread tissue damage from both infection and wasting releases Damage-Associated Molecular Patterns (DAMPs), which further amplify the inflammatory response. The result is not an acute, self-limiting inflammation, but a chronic, unremitting "cytokine storm" that becomes the central driver of the systemic pathology we observed. It is the force behind the constitutional symptoms, the metabolic derangements, and, critically, the endocrine collapse.

The intense catabolic pressure exerted by this inflammatory engine manifested as a profound metabolic collapse. Nearly half our cohort (48.4%) was underweight, a clinical sign of HIV wasting syndrome. This is a direct consequence of the inflammatory milieu. TNF-α, historically named 'cachectin', promotes skeletal muscle breakdown by upregulating the ubiquitin-proteasome pathway, a cellular system that tags proteins for degradation. This state of severe protein-energy malnutrition was biochemically confirmed by the low median serum albumin of 3.25 g/dL. Albumin is a negative acute-phase reactant; its synthesis by the liver is actively suppressed by cytokines like IL-6 to prioritize the production of acute-phase proteins such as C-reactive protein.[15] Thus, the hypoalbuminemia in our patients is a direct biochemical signature of this dual assault of inflammation and starvation. Similarly, the dyslipidemia observed in 81.3% of patients was not a result of diet but was a classic inflammatory signature. The pattern of low HDL cholesterol and high triglycerides is directly mediated by cytokines. TNF-α inhibits the action of lipoprotein lipase (LPL), the enzyme responsible for clearing triglycerides from the circulation, while simultaneously increasing hepatic VLDL (triglyceride) production. The anemia seen in 85.9% of the cohort is also best understood as anemia of chronic inflammation. The cytokine IL-6 stimulates hepatic production of the hormone hepcidin. Hepcidin is the master regulator of iron homeostasis; it functions by binding to and degrading ferroportin, the only known cellular iron exporter.[16] This action traps iron within macrophages and enterocytes, preventing its mobilization for use by the bone marrow in erythropoiesis. This sophisticated mechanism explains why simple iron supplementation is often ineffective in these patients. Each of these findings—wasting, hypoalbuminemia, dyslipidemia, and anemia—is not an independent problem but are

downstream consequence of the same core inflammatory process.

Our central hypothesis was that the hypothalamic-pituitary-gonadal (HPG) axis would be a primary casualty of this syndemic state, and our findings provide strong confirmation. The prevalence of hypogonadism was high (32.8% by total T, 42.2% by bioavailable T), and its etiology was overwhelmingly secondary (hypogonadotropic). This definitively points to a central failure of the hypothalamic-pituitary unit, rather than a primary testicular defect. The significant positive correlations between bioavailable testosterone and both CD4 count (ρ=0.35) and BMI (ρ=0.41) provide a clear statistical link: the more severe the immunodeficiency and the worse the nutritional state, the lower the patient's active testosterone level.[17] Pro-inflammatory cytokines act directly on the arcuate nucleus of the hypothalamus, inhibiting the pulsatile release of gonadotropin-releasing hormone (GnRH). A key molecular mediator in this process is the neuropeptide kisspeptin, a critical upstream activator of GnRH neurons. Kisspeptin-producing neurons are now understood to be the primary integrators of metabolic and inflammatory signals.[17] Their activity is potently suppressed by both inflammatory cytokines (like TNF-α) and metabolic stress signals (like low leptin), providing a precise molecular mechanism for the central shutdown of the reproductive axis. The severe malnutrition and low BMI in our cohort trigger an independent and powerful suppressive pathway. The hormone leptin, produced by adipose tissue, serves as a crucial signal to the brain about the body's energy stores. In a cachectic state, with depleted fat reserves, leptin levels plummet. As leptin is a key permissive signal for GnRH release, its absence is interpreted by the hypothalamus as a state of starvation.[18] The brain then initiates an adaptive shutdown of non-essential, energy-intensive processes like reproduction to conserve resources for immediate survival. This is a well-conserved evolutionary mechanism. It is crucial to interpret our findings within the broader context of NGIS. In any patient with a severe, acute illness (such as active TB or PCP), the body's endocrine axes undergo adaptive changes. The suppression of the reproductive and thyroid axes, alongside activation of the adrenal axis, is a hallmark of this response. Therefore, it is plausible that a portion of the secondary hypogonadism we observed represents a transient, adaptive state in response to the acute severity of the opportunistic infections. This does not diminish the importance of screening; rather, it adds a layer of critical clinical nuance. The finding of low testosterone in a patient with advanced HIV and an acute OI should prompt consideration for re-testing after the acute illness is treated before committing a patient to potentially lifelong testosterone replacement therapy.[18] This distinguishes between an adaptive state of sickness and a permanent pathological deficiency. Our use of calculated bioavailable testosterone strengthens these conclusions. In a population with low serum albumin and likely altered SHBG levels due to inflammation, total testosterone can be a misleading marker. By demonstrating an even higher prevalence of hypogonadism (42.2%) based on the physiologically active fraction, we provide a more accurate and clinically relevant estimate of true androgen deficiency in this cohort, moving the analysis closer to the biological reality at the tissue level.

The first domain detailed in Figure 5 outlines the profound metabolic chaos instigated by the disease. It begins by presenting the key clinical and laboratory findings that define this state: a high prevalence of wasting & malnutrition (48.4% underweight), near-universal anemia of chronic disease (85.9%), and widespread inflammatory dyslipidemia (81.3%). The figure then masterfully connects these findings to their underlying pathophysiology. The primary driver is identified as a cytokine storm, a state of chronic, high-level inflammation fueled by the virus and co-infections, with TNF-α and IL-6 cited as key mediators. This storm is directly responsible for the catabolic state that causes wasting and suppresses appetite. The anemia is explained by the action of the hepcidin hormone, whose production is stimulated by IL-6.[19] Hepcidin blocks the body's ability to mobilize and use

its iron stores, leading to a "functional" iron deficiency and impaired red blood cell production. Finally, the dyslipidemia is attributed to hepatic lipid reprogramming, where these same cytokines disrupt the liver's normal processing of fats, leading to the characteristic pattern of low protective HDL and high triglycerides.

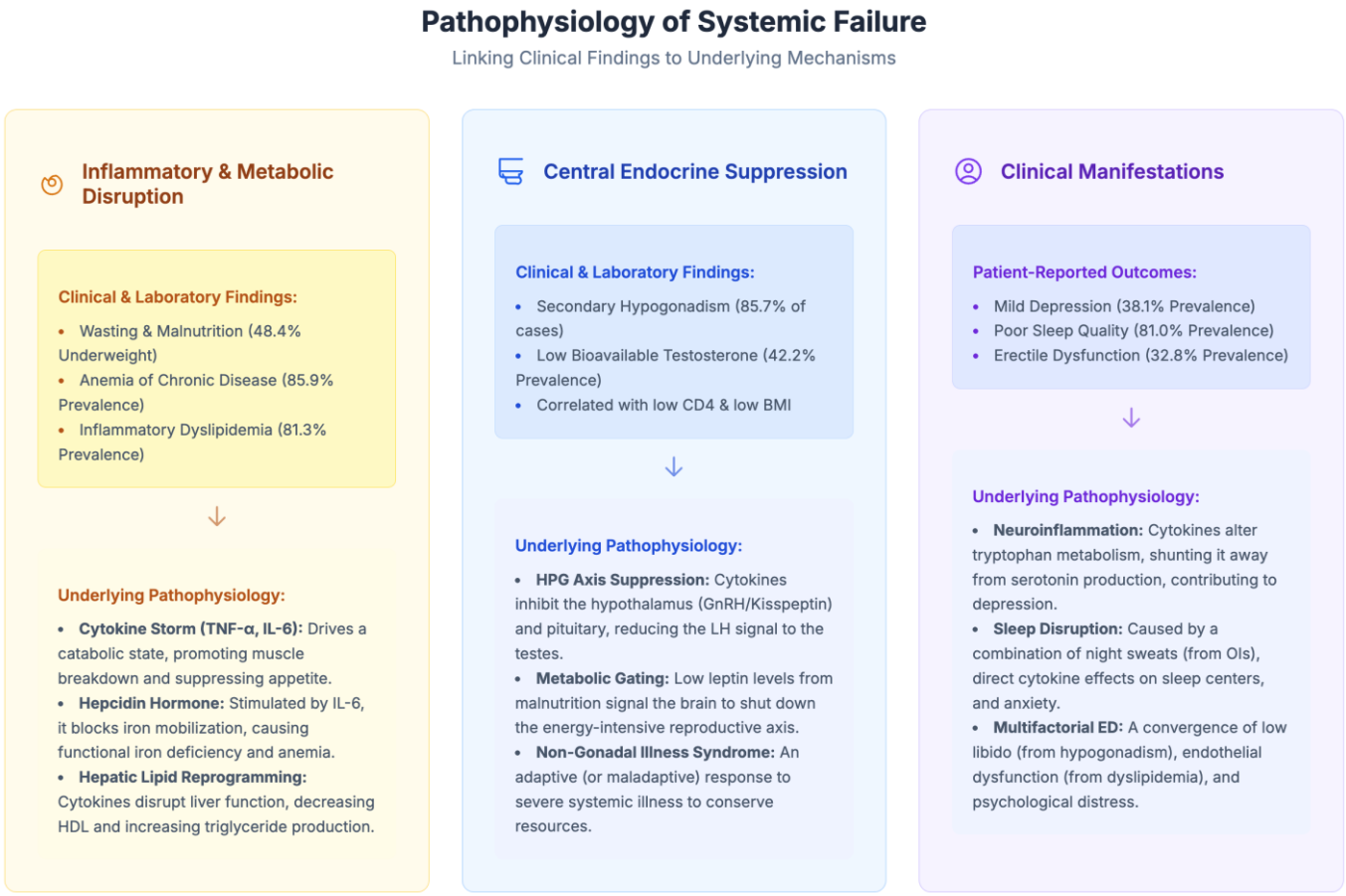

Figure 5. Pathophysiology of systemic failure.

This section of the figure illustrates how a single inflammatory trigger can produce multiple, seemingly disparate, metabolic abnormalities. The second domain of Figure 5 focuses on the endocrine system, demonstrating how it becomes a direct casualty of the systemic illness. The key findings presented are the high prevalence of low bioavailable testosterone (42.2%) and the fact that the vast majority of these cases (85.7%) are secondary hypogonadism, which is then shown to be correlated with low CD4 counts and low BMI. The figure explains this through a three-pronged mechanism. First is HPG axis suppression, where inflammatory cytokines directly inhibit the hypothalamus and pituitary glands, reducing the critical LH signal required for the testes to produce testosterone. Second is metabolic gating, a survival mechanism wherein low leptin levels resulting from malnutrition signal the brain to shut down the energy-intensive reproductive axis. Third, the figure introduces the crucial concept of non-gonadal illness syndrome, framing the endocrine suppression as an adaptive (or maladaptive) response to severe systemic

illness designed to conserve resources. This section expertly demonstrates that the hormonal failure is not a primary testicular problem but a central command failure orchestrated by the body's overwhelming response to inflammation and starvation. The final domain in Figure 5 translates the preceding physiological and biochemical disruptions into the patient's lived experience. It presents the key patient-reported outcomes: a high prevalence of mild depression (38.1%), poor sleep quality (81.0%), and erectile dysfunction (32.8%). Crucially, the figure provides a scientific explanation for each of these symptoms. The depression is linked to Neuroinflammation, where cytokines alter brain chemistry by shunting tryptophan metabolism away from the production of serotonin. The poor sleep quality is shown to be caused by a combination of physical symptoms from opportunistic infections (like night sweats), the direct effects of cytokines on sleep centers in the brain, and the psychological impact of anxiety. Finally, the erectile dysfunction is deconstructed into a Multifactorial problem, resulting from a convergence of low libido (from hypogonadism), endothelial dysfunction (from the inflammatory dyslipidemia), and psychological distress. This section provides a powerful conclusion to the narrative, showing how molecular and hormonal changes manifest as tangible, debilitating symptoms that severely impact the patient's quality of life.[19]

The profound physiological dysregulation documented in this study is not an abstract concept; it translates directly into a severely diminished quality of life for the patient. The questionnaire data provide a window into this lived experience, and the underlying pathophysiology offers a biological basis for their suffering. The pervasive poor sleep quality reported by 81% of the cohort is likely not a single issue but a final common pathway for multiple syndemic insults. The night sweats of tuberculosis physically disrupt sleep. Systemic cytokines, particularly TNF-α and IL-1, are known to alter sleep architecture, promoting light, fragmented sleep while suppressing restorative slow-wave sleep.[20] The anxiety of a new, life-threatening diagnosis and the hormonal imbalance of hypogonadism itself further contribute to insomnia. This chronic sleep deprivation inevitably contributes to the high rate of depressive symptoms (38.1%). Beyond the psychological burden, there is a direct biological link. Inflammatory cytokines can alter neurotransmitter metabolism in the brain, shunting the tryptophan pathway away from serotonin production (the "feel-good" neurotransmitter) and towards the production of neurotoxic metabolites like quinolinic acid. This provides a direct inflammatory mechanism for the development of depressive symptoms. The common finding of erectile dysfunction (32.8%) is similarly multifactorial. It stems from the central loss of libido due to low testosterone, but also from peripheral mechanisms. The inflammatory dyslipidemia contributes to endothelial dysfunction, impairing the nitric oxide-dependent vascular mechanisms required for a physical erection. This is compounded by the psychological distress of the diagnosis and the generalized fatigue and malaise of systemic illness. This illustrates that for the patient, the syndemic is experienced as a comprehensive collapse of their physical, mental, and sexual well-being. Addressing only the viral load with ART, while essential, is insufficient. The fatigue, depression, and wasting will persist if the underlying nutritional and endocrine failures are not also addressed. Our findings argue that a truly patient-centered approach requires a multi-pronged therapeutic strategy from the outset.

4. Conclusion

This study demonstrates that ART-naive men presenting with advanced HIV in this Indonesian setting are caught in a devastating syndemic of profound immunodeficiency, rampant opportunistic infections, severe malnutrition, and consequent endocrine collapse. The hypothalamic-pituitary-gonadal axis is a key casualty, with a high prevalence of secondary hypogonadism that is strongly and significantly linked to the severity of both immune depletion and nutritional wasting. The use of bioavailable testosterone provides a more accurate

and higher estimate of this androgen deficiency than total testosterone alone. These findings provide a powerful, evidence-based rationale for a paradigm shift in the initial management of HIV. A simple CD4 count and viral load are insufficient to capture the true burden of disease. We strongly advocate for the integration of comprehensive metabolic and endocrine screening—including, at a minimum, BMI, serum albumin, a lipid panel, and a baseline assessment of the HPG axis—into the standard of care for all men at the time of their HIV diagnosis. By identifying and addressing these critical, interconnected comorbidities from day one, clinicians can move beyond simply treating the virus and begin the work of holistically rebuilding the patient's health, improving their quality of life, and giving them the best possible chance for a successful long-term outcome.

5. References

1. Lachâtre M, Pasquet A, Ajana F, Soudan B, Lion G, Bocket L, et al. HIV and hypogonadism: a new challenge for young-aged and middle-aged men on effective antiretroviral therapy. AIDS. 2017; 31(3): 451–3.
2. Wong N, Levy M, Stephenson I. Hypogonadism in the HIV-infected man. Curr Treat Options Infect Dis. 2017; 9(1): 104–16.
3. Dutta D, Sharma LK, Sharma N, Gadpayle AK, Anand A, Gaurav K, et al. Occurrence, patterns & predictors of hypogonadism in patients with HIV infection in India. Indian J Med Res. 2017; 145(6): 804–14.
4. Khandwala YS, Raheem OA, Ali MA, Hsieh T-C. Variation in practice pattern of male hypogonadism: a comparative analysis of primary care, urology, endocrinology, and HIV specialists. Am J Mens Health. 2018; 12(2): 472–8.
5. Ranabir S, Nungsangla P, Premita M, Shaini, Singh B, Devi B, et al. Hypogonadism among HIV infected males and its correlation with CD4 count. J Evid Based Med Healthc. 2018; 5(34): 2507–11.
6. Pongener N, Salam R, Ningshen R, Visi V, Wairokpam T, Devi LS. A study on hypogonadism in male HIV patients in northeastern part of India. Indian J Sex Transm Dis AIDS. 2019; 40(1): 20–4.
7. Bajaj S, Sonkar KK, Verma S, Varma S, Singh AK. Assessment of glycemic status, Insulin Resistance and hypogonadism in HIV infected male patients. J Assoc Physicians India. 2020; 68(8): 43–6.
8. De Vincentis S, Decaroli MC, Fanelli F, Diazzi C, Mezzullo M, Morini F, et al. Health status is related to testosterone, estrone and body fat: moving to functional hypogonadism in adult men with HIV. Eur J Endocrinol. 2021; 184(1): 107–22.
9. Postel N, Wolf E, Balogh A, Obermeier M, Degen O, Mayr C, et al. Functional hypogonadism and testosterone deficiency in aging males with and without HIV-infection. Exp Clin Endocrinol Diabetes. 2021; 129(11): 798–802.
10. Pezzaioli LC, Quiros-Roldan E, Paghera S, Porcelli T, Maffezzoni F, Delbarba A, et al. The importance of SHBG and calculated free testosterone for the diagnosis of symptomatic hypogonadism in HIV-infected men: a single-centre real-life experience. Infection. 2021; 49(2): 295–303.
11. Santi D, Spaggiari G, Vena W, Pizzocaro A, Maggi M, Rochira V, et al. The prevalence of hypogonadism and the effectiveness of androgen administration on body composition in HIV-infected men: a meta-analysis. Cells. 2021; 10(8): 2067.
12. Quiros-Roldan E, Porcelli T, Pezzaioli LC, Degli Antoni M, Paghera S, Properzi M, et al. Hypogonadism and liver fibrosis in HIV-infected patients. J Endocrinol Invest. 2021; 44(9): 1971–9.

13. Pezzaioli LC, Porcelli T, Delbarba A, Maffezzoni F, Focà E, Castelli F, et al. Impact of hypogonadism on bone mineral density and vertebral fractures in HIV-infected men. J Endocrinol Invest. 2022; 45(2): 433–43.
14. Wu S, Hilton O, Pereira B, Girometti N, Milinkovic A, Ollandini G, et al. Correlation between different equations to calculate free testosterone for improved detection of hypogonadism in people living with HIV. Int J STD AIDS. 2022; 33(6): 613–7.
15. Lachâtre M, Pasquet A, Ajana F, Soudan B, Quertainmont Y, Lion G, et al. Hypogonadism: a neglected comorbidity in young and middle-aged HIV-positive men on effective combination antiretroviral therapy. AIDS. 2022; 36(8): 1061–71.
16. De Vincentis S, Rochira V. Update on acquired hypogonadism in men living with HIV: pathogenesis, clinic, and treatment. Front Endocrinol (Lausanne). 2023; 14: 1201696.
17. Lin K-Y, Sun H-Y, Liu W-D, Lin C-Y, Tsai M-J, Chuang Y-C, et al. Hypogonadism among HIV-positive men who have sex with men in Taiwan: Prevalence and associated factors. J Microbiol Immunol Infect. 2024; 57(5): 739–48.
18. Iddi S, Dika H, Kidenya B, Kalluvya S. Prevalence of hypogonadism and associated risk factors among newly diagnosed ART naïve HIV-infected males in Mwanza, Tanzania. Int J Endocrinol. 2024; 2024: 9679935.
19. Iddi S, Dika H, Kidenya BR, Kalluvya S. Serum gonadal hormones levels and hypogonadism in ART naïve newly diagnosed HIV infected adult males in Mwanza, Tanzania. BMC Endocr Disord. 2024; 24(1): 50.
20. Maffezzoni F, Porcelli T, Delbarba A, Pezzaioli LC, Properzi M, Cappelli C, et al. Hypogonadism and bone health in men with HIV. Lancet HIV. 2020; 7(11): e782–90.