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Lung function and its determinants among human immunodeficiency virus patients on antiretroviral therapy

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Abstract: HIV patients face an increased risk of lung impairment due to chronic inflammation and opportunistic infections, yet factors influencing abnormal lung function in those receiving antiretroviral therapy (ART) remain unclear. This cross-sectional study examined HIV-infected adults (≥18 years) on ART at Ngoerah Hospital (January-March 2025). Patients with active tuberculosis, respiratory infections, or spirometry contraindications were excluded. Participants underwent clinical evaluation and spirometry using Contec SP80B. Multivariate logistic regression identified risk factors for abnormal lung function. Among the 183 participants, 102 (55.74%) had normal lung function. Abnormalities included restrictive disorders (60 patients, 32.79%), obstructive disorders (8 patients, 4.37%), and mixed patterns (13 patients, 7.10%). A prior lung infection history was the sole independent risk factor for abnormal lung function (AOR 7.221; 95% CI: 2.444–21.336; $p < 0.001$). Age, sex, BMI, smoking, drug use, non-infectious lung disease history, HIV stage, CD4+ count, viral load, ART regimen, and treatment duration showed no significant associations ($p > 0.05$). Lung function abnormalities are prevalent among HIV patients on ART, with prior lung infections being a key determinant. These findings support the need for routine lung function monitoring in this population, particularly those with a history of lung infections.

Keywords: *Antiretroviral, Human immunodeficiency virus, Lung function, Spirometry.*

1. Introduction

Human Immunodeficiency Virus (HIV) is a chronic retroviral infection that progressively weakens the immune system, and it can lead to Acquired Immunodeficiency Syndrome (AIDS) [1]. The global prevalence of HIV continues to pose a significant public health challenge. According to the World Health Organization (WHO), an estimated 33.1 to 45.7 million people were living with HIV by the end of 2022, with the highest burden in Africa (39 million) [2]. In Indonesia, the HIV epidemic has evolved significantly over the past decade, with current cases distributed across multiple populations: 28.8% injection drug users, 25.8% men who have sex with men (MSM), 24.8% transgender individuals, 15.3% from the general population, and 5.3% female sex workers [2].

HIV infection can directly and indirectly impair lung function by disrupting pulmonary innate and adaptive immune responses. Direct HIV infection on bronchial epithelial cells will impair cell adhesion and trigger the release of pro-inflammatory mediators. In the adaptive immune system, HIV targets CD4+ T lymphocytes, leading to increased T-cell apoptosis and depletion of pulmonary T cells.

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Reduced CD4+ and elevated CD8+ T cells in the alveoli can result in lymphocytic alveolitis due to CD8+ cytotoxic T-cell activity [3]. Moreover, the resulting immune dysfunction increases susceptibility to opportunistic lung infections, further exacerbating lung injury and functional decline [4, 5].

Spirometry is a standard method for detecting lung function abnormalities, which are typically classified as obstructive or restrictive disorders based on the Forced Expiratory Volume in 1 second (FEV1) and the Forced Vital Capacity (FVC) [6]. Numerous studies have identified HIV as an independent risk factor for reduced lung function, with several contributing factors including age, sex, body mass index (BMI), smoking history, previous lung disease, CD4+ count, viral load, and antiretroviral therapy (ART) [7, 8]. However, findings remain inconsistent, particularly regarding the effects of ART on lung function.

Despite the growing body of international evidence, similar research in Indonesia is lacking. Given these considerations, this study aims to evaluate lung function and its determinants among HIV patients receiving ART at Ngoerah Hospital, a tertiary care center in Bali, Indonesia.

2. Methods

2.1. Study Design and Subjects

This cross-sectional study was conducted at the HIV/AIDS Care Center of Ngoerah Hospital between January and March 2025. The study population included HIV-positive individuals aged 18 years or older who had been receiving ART based on the Indonesian National Guidelines for Antiretroviral Therapy and HIV Management for at least six months. Patients with active pulmonary tuberculosis (TB), other ongoing respiratory infections, or contraindications to spirometry were excluded. All participants provided written informed consent prior to participation. The study protocol received ethical approval from the Ethics Committee of the Faculty of Medicine of Udayana University and Ngoerah Hospital, Bali, Indonesia (No. DP.04.03/D.XVII.2.2.219736/2025).

2.2. Study Procedure and Variables

After enrollment, participants underwent clinical assessment and spirometry testing using the Contec SP80B portable spirometer with a clean, disposable mouthpiece. All tests were conducted by a qualified pulmonologist following the standards set by the American Thoracic Society and European Respiratory Society (ATS/ERS). Only acceptable and reproducible spirometry curves were analyzed, using the average value from three valid measurements. Lung function status was interpreted based on FEV_1, FVC, and the FEV_1/FVC ratio. Obstructive lung disorder was defined as an FEV_1/FVC ratio of less than 70%, restrictive disorder as an FVC below 80% of the predicted value with a normal or elevated FEV_1/FVC ratio, and a mixed obstructive and restrictive lung disorder as both FEV_1/FVC<70% and FVC<80% [6]. Lung function status was further categorized into normal or abnormal (Presence of abnormal spirometry pattern).

Data on sociodemographic and clinical characteristics, including age, sex, body mass index (BMI), smoking status, history of illicit drug use, previous lung infection, chronic lung disease, baseline CD4+ T-cell count, baseline viral load, HIV clinical stage, ART regimen, and ART duration, were collected through medical history, physical examination, and chart review.

BMI was classified according to the WHO criteria adapted for the Asian population. For analytical purposes, BMI was further categorized into two groups: normal (18.5–22.9 kg/m²) and abnormal (underweight, overweight, or obesity). Underweight was defined as a BMI of less than 18.5 kg/m²; normal weight as a BMI between 18.5 and 22.9 kg/m²; overweight as a BMI between 23.0 and 24.9 kg/m²; and obesity as a BMI greater than 25.0 kg/m². Smoking status was classified as either smoker or non-smoker. A history of illicit drug use refers to the misuse or abuse of narcotics, psychotropics, or other addictive substances prior to HIV diagnosis. Prior lung infection was defined as any history of lung infection, such as pneumonia, TB, or pneumocystis pneumonia, occurring after HIV diagnosis.

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Chronic lung disease refers to non-infectious conditions such as asthma or chronic obstructive lung disease. Baseline CD4+ T-cell count and viral load were obtained from the initial laboratory results following HIV diagnosis, with CD4+ count classified as low (<200 cells/mm³) or high (≥200 cells/mm³), and viral load as low (<50 copies/mL) or high (≥50 copies/mL). HIV clinical staging was determined according to the World Health Organization criteria (stages I–IV). ART regimen was categorized as either NNRTI-based or non-NNRTI-based, and ART duration was classified as 6–12 months or more than 12 months.

2.3. Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical data. Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR), while categorical variables were expressed as frequencies and percentages. Dichotomous demographic and clinical data were then compared between HIV patients with normal and abnormal lung functions using the chi-square test. Variables with a p-value < 0.25 in the bivariate analysis were included in a multivariate logistic regression model to identify independent predictors of abnormal lung function. Statistical significance was determined at a p-value ≤ 0.05. All analyses were performed using SPSS version 25.0.

3. Results

A total of 183 HIV-positive patients receiving ART were included in this study. The majority of participants were male (69.40%), aged between 18 and 59 years (94.54%), employed (77.60%), had a normal body mass index (BMI) (62.30%), and were non-smokers (75.96%). Six participants (3.28%) reported a history of illicit drug use. Among them, one individual used marijuana (16.67%), one used methamphetamine (16.67%), two used both heroin and methamphetamine (33.33%), and two used a combination of marijuana and methamphetamine (33.33%). Forty-three patients (23.50%) had a documented history of lung infections, including three cases of pulmonary tuberculosis and four cases of Pneumocystis pneumonia (PCP). Only one patient reported a history of asthma. Most patients were classified under WHO clinical stages I or II (65.57%), had a baseline CD4+ T-cell count ≥200 cells/mm³ (68.31%), a baseline viral load <50 copies/mL (72.68%), and had been on ART for more than 12 months (95.36%). A comprehensive summary of the demographic and clinical characteristics of the study population is presented in Table 1.

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Table 1.
Characteristics of HIV patients on ART.

Characteristics	Total (n=183)
Age (years), mean ± SD	41.98 ± 9.81
18-59 years, n(%)	173 (94.54)
≥60 years, n(%)	10 (5.46)
Sex, n (%)	
Male	127 (69.40)
Female	56 (30.60)
BMI (kg/m²), mean ± SD	22.93 ± 3.59
Abnormal, n (%)	69 (37.70)
Normal, n (%)	114 (62.30)
Occupation, n (%)	
Housewife	15 (8.20)
Entrepreneur	4 (2.19)
Employee	142 (77.60)
Unemployed	22 (12.02)
Smoking status, n (%)	
Smokers	44 (24.04)
Non-smokers	139 (75.96)
History of Illicit drug use, n (%)	
Yes	6 (3.28)
No	177 (96.72)
Types of illegal drugs used, n(%)	
Marijuana	1 (16.67)
Amphetamine	1 (16.67)
Heroin + amphetamine	2 (33.33)
Marijuana + amphetamine	2 (33.33)
Prior lung infections, n (%)	
Yes	43 (23.50)
No	140 (76.50)
History of chronic non-infection lung disease, n (%)	
Yes	1 (0.55)
No	182 (99.45)
Baseline CD4 cell count, n (%)	
<200 cell/mm³	58 (31.69)
≥200 cell/mm³	125 (68.31)
Baseline viral load, n (%)	
≥50 copies/ml	50 (27.32)
<50 copies/ml	133 (72.68)
ART regimen, n (%)	
NNRTI	175 (95.63)
Non-NNRTI	8 (4.37)
ART duration, n (%)	
6-12 months	5 (2.73)
>12 months	178 (97.27)
WHO clinical stage, n (%)	
Stage I-II	120 (65.57)
Stage III-IV	63 (34.43)

ART, antiretroviral therapy; BMI, body mass index; NNRTI, Non-nucleoside reverse transcriptase inhibitors; SD, standard deviation; WHO, World Health Organization

Based on spirometry test results, 102 patients (55.74%) demonstrated normal lung function. Among the 81 patients (44.26%) with abnormal lung function, 60 (32.79%) exhibited a restrictive pattern, 8 (4.37%) showed an obstructive pattern, and 13 (7.10%) presented with a mixed restrictive and obstructive pattern. A detailed distribution of lung function status is presented in Table 2.

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Table 2.
Spirometry parameters and lung function status of HIV patients on ART.

Spirometry Parameters and Interpretation	**Total (n=183)**
FEV_1 (%prediction), median (IQR)	87,38 (74.88-96.79)
FVC (%prediction), median (IQR)	81,41 (73.24-89.79)
FEV_1/FVC ratio, median (IQR)	88,20 (81.50-94.60)
Lung function status, n (%)	
Normal	102 (55.74)
Abnormal	81 (44.26)
Restrictive pattern	60 (32.79)
Obstructive pattern	8 (4.37)
Mixed restrictive-obstructive pattern	13 (7.10)

FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; IQR, interquartile range

A comparison of demographic and clinical characteristics between HIV patients with normal and abnormal lung function is presented in Table 3. Smoking status, history of prior lung infection, WHO clinical stage, baseline CD4+ cell count, and baseline viral load were found to be significantly associated with abnormal lung function in HIV patients receiving ART ($p \leq 0.05$). Additionally, history of illicit drug use and ART regimen were identified as potential confounding variables ($p < 0.25$). These variables were included in a multivariate logistic regression model, as shown in Table 4.

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Table 3.
Comparison of demographic and clinical variables between HIV patients with normal and abnormal lung functions.

Determinants	Lung function		OR (95%CI)	p-value
	Abnormal (n=81)	Normal (n=102)		
Age (years), n (%)				
18-59 years	75 (43.4)	98 (56.6)	0.510	0.342
≥60 years	6 (60.0)	4 (40.0)	(0.139-1.873)	
Sex, n (%)				
Male	54 (42.5)	73 (57.5)	0.795	0.475
Female	27 (48.2)	29 (51.8)	(0.423-1.494)	
BMI, n (%)				
Abnormal	33 (47.8)	36 (52.2)	1.260	0.450
Normal	48 (42.1)	66 (57.9)	(0.693-2.299)	
Smoking status, n (%)				
Smokers	27 (61.4)	17 (38.6)	2.5	0.009*
Non-smokers	54 (38.8)	85 (61.2)	(1.246-5.015)	
History of illicit drug use, n (%)				
Yes	5 (83.3)	1 (16.7)	6.645	0.089
No	76 (42.9)	101 (57.1)	(0.761-58.055)	
Prior lung infections, n (%)				
Yes	36 (83.7)	7 (16.3)	10.857	<0.001*
No	45 (32.1)	95 (67.9)	(4.486-26.278)	
History of chronic non-infection lung disease, n (%)				
Yes				
No	1 (100)	0 (0)	-	0.443
	80 (44.0)	102 (56.0)		
WHO clinical stage, n (%)				
Stage III-IV	40 (63.5)	23 (36.5)	3.351	<0.001*
Stage I-II	41 (34.2)	79, (65.8)	(1.773-6.334)	
Baseline CD4 cell counts, n (%)				
<200 cell/mm^3	37 (63.8)	21 (36.2)	3.244	<0.001*
≥200 cell/mm^3	44 (35.2)	81 (64.8)	(1.695-6.208)	
Baseline viral load, n (%)				
≥50 copies/ml	29 (58.0)	21 (42.0)	2.151	0.022*
<50 copies /ml	52 (39.1)	81 (60.9)	(1.111-4.165)	
ART regimens, n (%)				
NNRTI	80 (45.7)	95 (54.3)	5.895	0.064
Non-NNRTI	1 (12.5)	7 (87.5)	(0.710-48.928)	
ART duration, n (%)				
6-12 months	2 (40.0)	3 (60.0)	0.835	1
>12 months	79 (44.4)	99 (55.6)	(0.136-5.123)	

Note: *statistically significance (p ≤0.05)
95%CI, 95% Confidence Interval; ART, antiretroviral therapy; BMI, body mass index; NNRTI, Non-nucleoside reverse transcriptase inhibitors; OR, Odds Ratio; SD, standard deviation; WHO, World Health Organization

Table 4.
Multivariate logistic regression model for risk factors of abnormal lung function in HIV patients on ART.

Risk Factors	AOR	95%CI	p-value
Smoking status (Smokers)	2.011	0.868-4.662	0.103
History of illicit drug use (Yes)	2.757	0.240-31.611	0.415
Prior lung infection (Yes)	7.221	2.444-21.336	<0.001*
WHO clinical stage (Stage III-IV)	0.840	0.335-2.105	0.711
Baseline CD4 cell count (<200 cell/mm^3)	2.088	0.914-4.772	0.081
Baseline viral load (≥50 copies/ml)	2.028	0.916-4.490	0.081
ARV regimens (NNRTI)	4.795	0.528-43.458	0.164

Note: *statistically significant (p≤ 0.05)
95%CI, 95% Confidence Interval; AOR, Adjusted Odds Ratio ART, antiretroviral therapy; BMI, body mass index; NNRTI, Non-nucleoside reverse transcriptase inhibitors; SD, standard deviation; WHO, World Health Organization

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After adjustment, prior lung infection emerged as the only significant independent risk factor for abnormal lung function among HIV patients on ART. Patients with a history of lung infection had a significantly 7-fold-higher risk of developing abnormal lung function than those without prior lung infection (AOR = 7.221; 95% CI: 2.444–21.336; $p < 0.001$). Conversely, smoking status ($p = 0.103$), history of illicit drug use ($p = 0.415$), WHO clinical stage III–IV ($p = 0.711$), baseline CD4+ cell count <200 cells/mm³ ($p = 0.081$), baseline HIV viral load ≥50 copies/mL ($p = 0.081$), and use of an NNRTI-based ART regimen ($p = 0.164$) were not significantly associated with abnormal lung function after adjustment.

4. Discussion

4.1. The Prevalence of Abnormal Lung Function in HIV Patients

Several studies have reported similar or lower rates of abnormal lung function among HIV patients. Baidya et al. found that 48% of ART-treated HIV patients in India had abnormal lung function, predominantly restrictive patterns [9]. Yeboah et al. reported a 32.9% prevalence of abnormal spirometry in South African patients, also with a predominance of restrictive disorders [10]. In contrast, a study in the United States found a 37% prevalence, with obstructive patterns being more common [7]. Van Riel et al. reported a lower prevalence (17.2%) in South Africa, with obstruction as the dominant pattern [11]. The differences in prevalence between studies may be due to population characteristics. Our study, Baidya, et al. [9] and Yeboah, et al. [10] focused on ART-treated patients, while Drummond, et al. [7] and Van Riel, et al. [11] included ART-naïve individuals. ART may improve immune status, lowering the risk of lung damage. However, ART can also trigger immune reconstitution inflammatory syndrome (IRIS), which may lead to lung inflammation and fibrosis [12]. Thus, differences in ART exposure and immune status may explain the differing patterns of lung function abnormalities across studies.

4.2. Determinants of Abnormal Lung Function in HIV Patients on ART

HIV infection can directly damage the respiratory epithelium and promote fibrotic tissue formation in the lung parenchyma, impairing lung function. Other contributing factors include host-related elements (age, smoking, drug use, history of lung infections or non-infectious lung diseases) and therapy-related factors (ARV duration and regimen) [4, 13, 14]. However, their direct impact on lung dysfunction remains controversial across studies.

In this study, age was not significantly associated with lung function abnormalities in HIV patients on ART ($p=0.342$), aligning with findings from Yeboah, et al. [10]; Van Riel, et al. [11] and Baidya, et al. [9]. Conversely, Drummond, et al. [7] and Gupte, et al. [15] found that older age increased the risk of lung dysfunction. Physiologically, aging leads to reduced chest wall and respiratory muscle strength and reduced lung elasticity, causing a gradual decline in lung function, particularly after age 65 [16, 17]. However, this study was dominated by young patients with only 10 patients aged ≥60, limiting the observable impact of age-related lung function decline.

Our study found no significant association between sex and lung function abnormalities in HIV patients on ART ($p = 0.475$), similar to findings by Gupte et al., which focused on obstructive disorders. However, Baidya, et al. [9] and Yeboah, et al. [10] reported that female sex significantly increased the risk of restrictive lung impairment in HIV patients on ART. Physiologically, males typically have larger airways and lung capacities than females of the same age and body weight, and are less prone to lung function abnormalities when fibrotic tissue forms. Females, however, experience greater muscle mass loss when affected by HIV-related weight loss, which may increase their risk of lung dysfunction [16]. This could explain the higher incidence of lung function abnormalities observed in female HIV patients in some studies [9, 10]. In our study, most patients were young, had normal BMIs, and received ART. Thus, female patients may not have experienced significant muscle mass loss due to aging or malnutrition, leading to comparable lung function to male patients.

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In this study, BMI was not significantly associated with lung function in HIV patients on ART ($p = 0.450$), consistent with findings from Van Riel, et al. [11]; Gupte, et al. [15] and Yeboah, et al. [10] where BMI also showed no significant effect. However, Baidya et al. found that underweight increased the risk of restrictive lung disorders [9]. The impact of BMI on lung function remains debated. While excess abdominal fat accumulation in obese patients can reduce tidal volume and airflow due to diaphragmatic displacement, the significant effect is only found in morbidly obese patients. Meanwhile, malnutrition in an underweight individual may impair lung function through loss of respiratory muscle mass and increased systemic inflammation [9, 16]. The lack of association in this study may be due to most participants having normal BMI, with few underweight individuals and none with morbid obesity.

Our study found that smokers had a higher prevalence of abnormal lung function (61.4% vs. 38.8%), but smoking was not a significant risk factor after adjusting for other variables ($p = 0.103$). This aligns with findings by Van Riel, et al. [11] and Baidya, et al. [9]. Meanwhile, other studies, such as Drummond, et al. [7] and Sampériz, et al. [18] reported increased risk in heavy smokers (>30 pack-years). Smoking contributes to lung damage via oxidative stress, epithelial injury, and inflammation, but its impact varies with smoking intensity and age. Most studies rely on self-reported smoking status, which may introduce bias. Additionally, the detrimental effects of smoking on lung function become more pronounced in older HIV patients, typically over 50 years, but are less evident in younger populations [3, 19].

The history of illicit drug use was not associated with abnormal lung function in our study ($p=0.089$). This is consistent with findings by Drummond, et al. [7] and Simonetti, et al. [20] who also reported no significant association. However, Gingo et al. [21] found that injection drug use increased the risk of obstructive lung disease in HIV patients by 2.87 times [21]. The association between illicit drug use and lung function abnormalities is controversial, as many drug users are also smokers, which is known to have adverse effects on lung function. Cocaine use, particularly via inhalation, can lead to diffusion impairments in the lungs due to direct toxicity in the alveoli. Heroin use may increase the risk of pneumonia, which could further lead to lung fibrosis in HIV patients. Amphetamine may cause lung barotrauma and acute lung edema when inhaled, while marijuana is associated with acute bronchodilation and chronic side effects like increased sputum production [21]. While illicit drug use may have indirect effects, such as through smoking or inhalation, these studies are limited, and more research is needed to clarify the impact of inhaled or snorted drugs on lung function, as most studies only assessed injection drug use.

A history of lung infections was found to be a significant risk factor for abnormal lung function in HIV patients receiving ARV therapy, even after adjusting for other factors. Similar findings were reported by Van Riel, et al. [11] and Zifodya, et al. [14] where a history of pneumonia and TB increased the risk of abnormal lung function. In their study, a history of pneumonia increased the risk of obstructive lung disease by 1.4 times and restrictive lung disease by 2.4 times. A history of TB increased the risk of obstructive lung disease by 2.5 times and restrictive lung disease by 3.0 times [7, 14] also found that a history of PCP and bacterial pneumonia was linked to lung dysfunction [7]. Pathogen invasion of the lungs could trigger neutrophil recruitment to the site of infection and initiate the release of local and systemic inflammatory cytokines, including interleukin (IL)-4, IL-6, IL-10, IL-8, IL-1β, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β. Uncontrolled lung inflammation in immunocompromised patients can lead to severe parenchymal damage, tissue remodeling, pulmonary fibrosis, and pulmonary dysfunction. Besides, chronic inflammation from HIV and uncontrolled tissue remodeling after inflammation due to infection can lead to bronchiectasis and bronchial obstruction. Therefore, a history of lung disease, including pneumonia and TB, is associated with a higher risk of lung function abnormalities in HIV patients [4, 5].

This study found no significant association between a history of non-infectious lung disease and lung function in people living with HIV. In contrast with our study, Drummond et al. reported that asthma history increased the risk of obstructive lung disease in HIV patients, though not with restrictive lung disease [7]. Similarly, Gingo et al. [22] found significant associations between both

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asthma and COPD and obstructive lung disorder in HIV patients [22]. A history of asthma or COPD increases the risk of lung dysfunction in HIV patients due to chronic airway inflammation. HIV infection further amplifies inflammation, contributing to lung damage and impaired function [22]. COPD is also linked to reduced baseline lung function, elevating long-term risk. Auld et al. identified baseline impairment as a strong predictor of dysfunction after 12 months of ART [12]. However, there was only one patient with a history of asthma in our study, which limits the ability to detect significant associations.

This study observed a higher prevalence of abnormal lung function in patients with WHO clinical stages III–IV than in clinical stage I–II (63.5% vs. 34.2%). However, the association was insignificant after multivariate adjustment. Sampériz, et al. [18] using CDC classifications, found that stage C HIV significantly increased the risk of obstructive lung disorder [18]. Advanced HIV stages often involve more severe infections and wasting syndrome, which reduce respiratory muscle mass and contribute to both obstructive and restrictive lung conditions [3, 23]. Consequently, the initial association between WHO clinical stage and lung function abnormalities lost significance after adjusting for BMI, prior lung infections, baseline viral load, and CD4 cell count.

Although high baseline viral load (≥50 copies/mL) and low CD4 count (<200 cells/mm^3) were significantly associated with lung function abnormalities in our study, both lost significance after adjustment ($p = 0.081$). Consistent with our findings, Drummond, et al. [7] and Gupte, et al. [15] also found no significant association between these markers and lung function. In contrast, Azezew, et al. [24] reported correlations with FEV1 decline, though their analysis was limited to a single parameter and post-ART measurements [24].

A high baseline viral load (≥50 copies/mL) and low CD4 cell count (<200 cells/mm^3) are indicative of advanced HIV infection, which increases susceptibility to opportunistic infections, including lung infections. These infections can lead to lung damage and contribute to lung function abnormalities [7, 13]. Thus, in this study, baseline viral load and CD4 cell count were no longer significantly associated with abnormal lung function after multivariate adjustment.

The relationship between ART exposure and lung function abnormalities in people living with HIV remains controversial. Some studies suggest ART has a protective effect by reducing HIV-related airway damage and opportunistic infections, while others indicate that ART may accelerate lung dysfunction [5, 13].

In this study, ART duration was not associated with lung abnormalities. These findings was consistent with studies by Gupte, et al. [15]; Van Riel, et al. [11] and Yeboah, et al. [10] which also found no link between ART duration and lung function. However, Azezew, et al. [24] found a negative correlation between ART duration and FEV1, though their study assessed only this single parameter [24].

The mechanisms underlying the influence of ART on lung function are still debated. ART has been associated with irreversible airway obstruction, though direct lung toxicity has not been confirmed. Proposed mechanisms include increased airway inflammation and oxidative stress. ART may reduce the expression of peroxisome proliferator-activated receptors (PPARs), which play anti-inflammatory roles in the lungs. Reduced PPAR expression can enhance inflammation [21]. Most ART regimens also produce reactive oxygen species (ROS), contributing to oxidative stress, a key factor in lung damage [25].

ART may also trigger immune-mediated lung injury. For instance, immune reconstitution inflammatory syndrome (IRIS) can cause hyperinflammation in response to residual lung antigens, leading to parenchymal damage [26]. Other theories include ART-induced autoimmunity involving lung-specific antigens [5]. Despite these risks, the protective effect of ART on lung function is the subject of an ongoing debate.

NRTIs, NNRTIs, and PIs have distinct mechanisms, but all may contribute to oxidative stress by increasing ROS production. NRTIs impair mitochondrial DNA replication, NNRTIs disrupt the respiratory chain, and PIs interfere with mitochondrial enzymes and may reduce antioxidant capacity

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Harshithkumar, et al. [25] and Schank, et al. [27]. Kunisaki, et al. [28] reported higher oxidative stress in patients on PI-based and triple-drug regimens, suggesting non-NNRTI regimens may pose a greater risk for lung dysfunction [29]. However, our study also found no significant association between ART regimens and lung function abnormalities, consistent with Kunisaki, et al. [28]. The lack of association may reflect the multifactorial nature of ART-related lung impairment and the limited number of patients on non-NNRTI regimens. Thus, further studies are needed to explore the association of the ART regimen with lung function.

4.3. Advantages and Disadvantages

Our study had a relatively large sample and assessed various potential contributing factors, from host-related variables to therapy-related ones. The findings of this study may serve as a reference for future research aiming to explore, in greater detail, the determinants of lung function abnormalities among HIV patients in Indonesia. However, this study has some limitations. Lung function abnormalities were not analyzed based on obstructive, restrictive, and mixed obstructive-restrictive as separate outcomes. As a result, the identified risk factors reflect associations with overall lung function abnormalities, rather than specific types of abnormal lung function.

5. Conclusion

Lung function abnormalities are common among people living with HIV, even in those receiving ART. The mechanisms underlying impaired lung function in this population are complex and multifactorial. This study identified a prior history of lung infections as a key determinant of lung function abnormalities in HIV patients. We hope that these findings can serve as a reference for future studies that try to understand the lung impairment in HIV patients.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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