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ORIGINAL RESEARCH

# Association of Substance Use with Immunological Response to Antiretroviral Therapy in HIV-Positive Patients from Southwest Ethiopia: A Prospective Observational Study

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**Background:** Use of psychoactive substances by HIV-positive patients in the course of antiretroviral drug treatment has become a public health problem globally. Substance use (alcohol, nicotine, and khat) during the course of treatment results in interactions with drugs that lead to undesired treatment outcomes. This condition is understudied, and the consequences of substance use among patients on antiretroviral treatment are not well explored.

**Methods:** A prospective observational study was conducted among people on antiretroviral therapy (ART) at Jimma University Medical Center in southwest Ethiopia from April 20 to November 27, 2019. Data were collected using the World Health Organization's alcohol, smoking, and substance involvement screening test among adults who have followed antiretroviral therapy for a minimum of 6 months. Logistic regression analysis was done to identify factors associated with immunological response. The inadequate immunological response was defined as patients who were unable to achieve or maintain a CD4 cell count of >350 cells/mm³ after the 6-months of follow-up.

**Results:** Of the 332 patients enrolled, a majority (64.2%) of the respondents were females. The mean (±SD) age of the patients was 38.5 ± 9.5 years. The proportion of participants with a high level of health risk due to alcohol use was 8.4%, while 63.8% of them were non-alcohol users with no health risk. In multivariable logistic regression analysis, moderate and high levels of health risks from alcohol use were significantly associated with increased odds of inadequate immunological response (AOR: 2.9; 95% CI, 1.1–7.4) and (AOR: 4.3; 95% CI, 1.2–14.8), respectively, but the level of health risk from khat and cigarette use showed no association with inadequate immunological response in this study.

**Conclusion:** Moderate and high levels of health risk from alcohol use were independently associated with inadequate immunological response. People living with HIV/AIDS should regularly be screened for and be educated about substance use and its potential negative impact on CD4 cell recovery.

**Keywords:** substance use, antiretroviral therapy, immunological response, HIV/AIDS

## Background

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) patients always have intercurrent health-associated issues: opportunistic infections, chronic inflammation, mental health conditions, medication side effects, and substance-use disorders, which result from immune suppression, treatment effects, shared risk factors, or disease processes.[1] Incomplete immunologic response (CD4 <350 cells/μL) despite antiretroviral therapy (ART) was associated with an increased risk of mortality and morbidity.[2–6] CD4+ cell count recovery is diminished in East Africa, and the observed differences are significant enough to influence clinical outcomes.[7] To achieve an optimal immunological response from antiretroviral therapy, firm assessment, and control of all determinants is mandatory.[8–14]

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Substance use among people living with HIV/AIDS (PLWHA) has raised many concerns associated with key therapeutic indices of treatment. However, study findings in this area are limited and inconsistent with their outcomes. In addition to increasing the risk of exposure to HIV/AIDS, ongoing substance use harms ART initiation, disease progression, immunological response, and compliance with medication.[8] Studies showed the importance of assessing, monitoring, and targeting ongoing substance use in PLWHA to aid medication adherence. The use of a substance as a way of coping with stress increases the risk of medication non-adherence.[15]

Daily or greater frequency of crack cocaine use exacerbates HIV/AIDS disease severity independent of antiretroviral therapy, but further investigation is recommended because of the underlying biological mechanism or other factors attached to crack cocaine use.[16] A higher HIV viral load was seen at times of crack cocaine use in a longitudinal pattern of illicit drug users.[17] A recent review showed that active substance use is one of the major determinants of poor adherence to ART.[18] Sub-optimal medication adherence has been observed among HIV/AIDS patients who use addictive drugs, or alcohol in a dose–response fashion of association between alcohol use and ART nonadherence is observed.[18]

Alcohol use alters the effectiveness of ART by weakening the immune system,[19] its effects on drug metabolism, and medication adherence.[20] Moderate alcohol use among those with CD4 >200 cells/mm³ did not affect the rate decline of CD4 cells to ≤200 cells/mm³ after 30 months compared to abstainers. Frequent alcohol users (two or more drinks daily) were three times more likely to present a decline of CD4 to ≤200 cells/mm³.[21] People with alcohol dependence were nine times more likely to have CD4 ≤ 200 cells/mm³.[22] The median CD4 cell count among habitual alcoholics, social alcoholics, and non-alcoholics was 168.3, 238.1, and 226.6, respectively.[23] However, more advanced HIV/AIDS disease severity is associated with long-term patterns of persistent unhealthy alcohol use.[24]

One cohort study conducted in Switzerland reported that 52.3% of adult retroviral-infected patients used alcohol in the past 6 months.[25] In southern Brazil, 28.6% of PLWHA had alcohol abuse in the last year.[26] In sub-Saharan Africa, the prevalence of unhealthy alcohol use among PLWHA was 32.2%.[27] In Ethiopia, 27.5% of PLWHA used a substance at least once in their lifetime, and Alcohol was the primary abused substance.[28] In Jimma, 32.6% of PLWHA had alcohol use disorder.[29]

The nicotine present in tobacco, which is an enzyme inducer, is predominantly metabolized by hepatic cytochrome P450 2A6 (CYP2A6) and CYP3A4, which metabolizes approximately half of the commercially available drugs including ART. The association between cigarette smoking and ART outcomes has been inconsistent.[30–32] A prospective study in America revealed a significant baseline smoking-by-time interaction effect for low CD4 cell count.[33] In Russia, recent cigarette use was independently related to unsuppressed viral load, but there were no significant differences in CD4 cell count.[34] But in Boston, there was no association between cigarette use and HIV/AIDS disease progression, as measured by CD4 cell count and viral load.[35]

A cross-sectional study in Jimma showed that there was an association between khat use and missing at least one dose of ART medication in the preceding month,[36] and its use has also been associated with an increased prevalence of smoking and alcohol use.[37] In Jimma, even though it is a high-burden area for substance use, there is no data in Jimma and Ethiopia, which showed an association between the level of health risk alcohol, cigarette, and khat use with immunological recovery.

Despite the overall effect of substance use on ART response, its effect is still controversial because of the unclear effect of substances and presumed non-adherence. Also, the currently available evidence literature has shown discrepancies in findings for factors affecting immunologic response and there is no conclusive evidence of the association between substance use and immunological response. Studies in Ethiopia have shown the prevalence of alcohol, khat, and cigarette use among RVI patients, and two other studies also showed the risk level of alcohol use, but in our population/setting yet no study has shown the association between the level of health risk substance use and HIV disease progression. Therefore, the main aim of this study was to determine the association between substance use and immunological response.

# Method

## Study Setting

This study was conducted at Jimma University Medical Center (JUMC) in southwest Ethiopia between April and November 2019. JUMC is the only referral hospital in the southwestern part of the country and provides fee-free services

for PLWHA. An outpatient treatment service for HIV was established in 2005. Since 2017 antiretroviral therapy is initiated for all clients tested HIV positive regardless of their CD4 level (with the principle of test and treat). A total of 5518 people with HIV/AIDS were registered at the JUMC ART treatment center. Since 2019, about 3217 patients are on ART and 2953 of them are adults aged ≥18 years.

## Study Design

A hospital-based prospective observational study was used.

## Study Subject

The study subjects were adult PLWHA who have followed treatment for a minimum of 6 months at JUMC. Severely ill patients who required emergency medical help were excluded.

## Sample Size and Sampling Technique

The sample size for this study was determined for both Inadequate immunological response (CD4 ≤350 cells/mm$^3$) among adult RVI patients on ART and substance use among RVI patients. To obtain the maximum sample size for our study. We used the maximum calculated sample size from the two, based on a single population proportion formula, a 95% confidence interval and proportion (p) taken as 27% for poor treatment outcome (CD4 ≤350 cells/mm$^3$) among adult RVI patients on ART by Stefanie Kroeze in sub-Saharan Africa, 2018,[2] which gives the maximum sample size from prospective studies with similar outcome measure to our study

$$n = \frac{(Z_{\alpha/2})^2 p(1-p)}{d^2}$$

Where: z = standard score corresponding to 95% CI=1.96

p = proportion of poor treatment outcome among RVI patients on HAART = 0.27

d = Margin of error/precision = 5%

$$n = \frac{(1.96)^2 (0.27)\ (0.73)}{(0.05)^2} = 303$$

According to the smart care database of the ART clinic, since the source population was 2953 which is less than 10,000 populations the correction formula was used.

- n\(1+n/N) = 303/(1+ 303/2953) = 276, then when adjusted for 27.6 (10%) non-response.

The sample size was found to be 304.

Also, by using single population proportion formula, with a 95% confidence interval and a proportion (p) of 32.6% for alcohol use among PLWHA by Matiwos Soboka at JUMC in 2014,[29] that gives the maximum sample size from the studies conducted on substance use among RVI patients on ART, the sample size was calculated and found to be 332.

Therefore, the maximum calculated sample size from the two (332) was considered the final sample size for this study.

A consecutive sampling technique was used. During the participant recruitment period (April 20 to May 19, 2019), all eligible adult clients of the ART clinic were invited and enrolled consecutively until the calculated sample size was obtained.

## Study Variables

### Outcome/Dependent Variable

Immunological response (CD4 cell count).

## Main Exposure/Independent Variable

### Substance Use-Related Factors

Alcohol use health risk level, cigarette use health risk level, khat use health risk level.

## Covariates/Confounders

### Patient Related-Factors

Age, sex, residence, BMI, marital status, occupation, educational level, functional status, follow-up frequency in months.

## Treatment-Related-Factors

Baseline ART adherence, current adherence, treatment duration in months, initial regimen, current regimen, ever switched regimen, single tablet regimen, co-medications.

## Clinical Related-Factors

Baseline CD4 cell count, viral load, co-morbidities, TB history/OIs, new/recurrent OIs, hemoglobin level, WHO treatment stage.

## Data Collection Instrument and Procedures

### Exposure Variable

The level of health risk from substance use was measured by using the WHO alcohol, smoking, and substance involvement screening test (ASSIST),[38] validated for use in primary care settings.[39] By the recommended scoring from 0 to 27+, scores in the mid-range on the ASSIST are likely to indicate hazardous or harmful substance use ("moderate risk") and higher scores are likely to indicate substance dependence ("high risk"). Questions particularly associated with dependent or "high risk" use are a compulsion to use (question 3), failed attempts to cut down (question 7), and injecting behaviour (question 8).

Level of Health risk Alcohol Use: (0–10 low, 11–26 moderate, and 27+ high risk of health and other problems from current pattern of use).

Level of Health Risk Tobacco Use: (0–3 low, 4–26 moderate 27+ high risk of health and other problems from current pattern of use).

Level of Health Risk Khat Use: (0–3 low, 4–26 moderate, 27+ high risk of health and other problems from current pattern of use).

If the patient never used either khat or alcohol or cigarette in his/her lifetime he/she was considered as having no health risk for the substance he/she never used.[38]

A pre-tested structured questionnaire adapted from a review of related literature that contains patient, clinical, and treatment-related factors was applied to all participants. All participants voluntarily participated and signed informed consent forms before enrollment in the study. A face-to-face interview was conducted by five data collectors specifically selected from the ART clinic.

Data were coded by assigning a three-digit unique identification number, but together with this, a five-digit unique ART clinic card number was also used as a supportive identification tool. Information regarding patient and substance use-related factors was obtained from an interview during the participant recruitment period (April 20 to May 19). Applying the recommended cutoff points, the score obtained from ASSIST was grouped into four predefined health risk groups no risk, low, moderate, and high.

## Outcome Variable

### Immunological Response

Immunological response was measured after six months of the follow-up period. For all the patients included in the analysis, CD4 cell counts were done during the follow-up period from May 20 to November 27, 2019, and taken as the measure of immunological response.

### Adequate Immunological Response

Patients who achieved or maintained a CD4 cell count of >350 cells/mm$^3$ during the 6-months of follow-up.

### Inadequate Immunological Response

Patients who were unable to achieve or maintain a CD4 cell count of >350 cells/mm$^3$ during the 6 months of follow-up.[40]

Data on baseline ART history were collected from documented medical records. The most recently documented CD4 cell count was taken as baseline CD4 cell count for this study, baseline CD4 cell count measurements were conducted within the year of the study (mean of 3 months).

The immunological response was measured every six months with BD FACSpresto™ cartridge by the Hospitals antiretroviral therapy clinic laboratory unit with a staff of BSc in laboratory science and MSc in immunology, and samples were analyzed by using BD FACSPresto™ cartridges with finger-stick samples. The fingertip is punctured with the lancet, and then the first drop of blood is wiped. The second drop of blood is added into the inlet port of the cartridge. The finger is cleaned, the cartridge is capped, and a bandage is applied to the finger. Baseline plasma HIV-1 RNA load was measured by COBAS® AmpliPrep.

## Adherence

Adherence = Number of doses of HAART taken ÷ Number of prescribed doses of HAART × 100%

Good adherence, >95%, fair adherence, 85–95%, and poor adherence, <85% doses taken.[13,41,42] From the HIV care ART follow-up form, the documented adherence of participants from their most recently documented CD4 cell count was measured up to the date of enrolment of participants and was taken as baseline adherence. During the follow-up period, we followed the participants till their CD4 cell counts were conducted. We registered adherence at each follow-up visit. Then, for analysis purposes, we classified adherence as (Good adherence if >95% doses were taken at every follow-up visit, Poor if at least one ≤95% adherence was encountered at the follow-up visit).[43] New/recurrent opportunistic infections were considered if the patient was initiated on treatment for that opportunistic infection.

## Data Processing and Analysis Procedures

The collected data were entered into Epi-data version 3.1 then cleaned and exported to SPSS version 21 for analysis. Descriptive statistics were used to show the distribution of frequency. The analysis was performed using bivariate and multivariate logistic regression. Independent variables with a P-value of less than 0.25 in bivariate analysis were included in backward step regression. The overall statistical significance of the model was reported by adjusted odds ratios (AOR) with its corresponding 95% confidence interval, a p-value <0.05 was considered statistically significant.

# Results

## Socio-Demographic Characteristics

A total of 332 participants were enrolled in this study, and two-thirds (64.2%) of the participants were females. The mean (±SD) age of the patients was 38.58 ± 9.5 years. Thirty-nine of them were above 50 years. The mean (±SD) weight was 60.46 kg (9.84 kg). Currently, most (73.8%) of the participants were urban residents. Married (52.4%), employed (36.7%), secondary education (35.8%), and 17.2% were underweight BMI (<18.5kg/m²). All clients had regular follow-up frequency: 82 (24.7%), 157 (47.3%), 58 (17.5%), and 35 (10.5%) everyone, two, three, and six months, respectively (Table 1).

## Clinical Characteristics

### Disease-Related Characteristics

At enrolment, about 88.6% of study participants were on WHO clinical stage I, followed by WHO clinical stage II (9.6%), and TB history/opportunistic infection among 42 (12.7%), Co-morbidity among 68 (20.5%) (Table 2).

## Treatment-Related Characteristics

An initial ART regimen of (TDF+3TC+EFV) 59.9% followed by (AZT+3TC+NVP) 22.3%, (TDF+3TC+NVP) 5.4%, (AZT +3TC+EFV) 4.8%, (D4T+3TC+EFV) 3.9%, (D4T+3TC+NVP) 3%, while the current ART regimens are (DTG+3TC+TDF) 5.7%, (TDF + 3TC + EFV) 62.7%, (AZT+3TC+NVP) 16.9%, and (TDF+3TC+ATV/r) 1.8%. The minimum duration of ART at enrolment in this study was eight months, with a mean (±SD) of 74.2 (±36.6) months. Currently, the majority (68.4%) of participants were on a single tablet regimen (TDF+3TC+EFV and DTG+3TC+TDF). In line with this, 96.1% were on the first-line regimen. Overall, 65 (19.6%) had a history of switched regimens (before and during the study). The main reason for switching was suspected toxicity 28 (8.4%) followed by better first-line available 25 (7.5%). Those drugs responsible for

**Table 1** Sociodemographic Characteristics of PLWHA in Jimma University Medical Center, 2019

| Variable | Category | Frequency n (%) |
|---|---|---|
| Sex | Male | 119 (35.8) |
| | Female | 213 (64.2) |
| Asge (years) | ≤ 50 | 293 (88.3) |
| | >50 | 39 (11.7) |
| Residence | Rural | 87 (26.2) |
| | Urban | 245 (73.8) |
| Marital status | Married | 174 (52.4) |
| | Single | 51 (15.4) |
| | Widowed | 35 (10.5) |
| | Divorced | 72 (21.7) |
| Educational status | No formal education | 37 (11.1) |
| | Primary (1–8) | 119 (35.8) |
| | Secondary (9–12) | 119 (35.8) |
| | College and above | 57 (17.2) |
| Occupation | Daily laborer | 76 (22.9) |
| | Employed at government/private/self | 122 (36.7) |
| | Student | 9 (2.7) |
| | Farmer | 11 (3.3) |
| | Unemployed | 46 (13.9) |
| | Housewife | 61 (18.4) |
| | Retired | 7 (2.1) |
| BMI | ≥18.5 | 275 (82.8) |
| | < 18.5 | 57 (17.2) |
| Functional status | Working | 309 (93.1) |
| | Ambulatory | 23 (6.9) |
| Frequency of follow-up (in months) | One month | 82 (24.7) |
| | Two month | 157 (47.3) |
| | Three month | 58 (17.5) |
| | Six month | 35 (10.5) |

**Table 2** Baseline and Follow-Up Clinical Related Characteristics of PLWHA in Jimma University Medical Center, 2019

| Variable | Category | Frequency n (%) |
|---|---|---|
| Baseline CD4 cell count > 350 cells/mm$^3$ | Yes | 273 (82.2) |
| | No | 59 (17.8) |
| Viral load <1000 copies/mL | Yes | 297 (89.5) |
| | No | 35 (10.5) |
| WHO treatment stage | T1 | 294 (88.6) |
| | T2 | 32 (9.6) |
| | T3 | 6 (1.8) |
| Hemoglobin level | < 12 | 131 (39.5) |
| | ≥ 12 | 201 (60.5) |
| TB history/opportunistic infection | Yes | 42 (12.7) |
| | No | 290 (87.3) |
| New/recurrent opportunistic infections | Yes | 16 (4.8) |
| | No | 316 (95.2) |
| Co-morbidity | Yes | 68 (20.5) |
| | No | 264 (79.5) |

suspected toxicity were D4T and AZT by 22 (6.6%) and 5 (1.5%), respectively. Meanwhile, at the time of the current study, DTG+3TC+TDF 19 (5.7%) was the most commonly switched regimen (Better first line available). Of patients with viral load ≥1000 copies/mL, 17 (48%) and 14 (40%) had poor enrolment and current adherence, respectively (Table 3).

## Immunological Response

Out of 332 clients, all had their CD4+ cell count measured during the observation period. From which assessment of immunological response revealed 261 (78.6%) had $CD_4$ cell count of >350cells/m³ and 71 (21.4%) showed $CD_4$ cell count ≤350 cells/$mm^3$.

## Association of Substance Use and Other Variables with Immunological Response

In bivariate analysis, $CD_4$ cell count ≤350 cells/$mm^3$ was significantly associated with moderate health risk level alcohol use (p = 0.02), high health risk level alcohol use (p = 0.01), and moderate health risk level cigarette use (p = 0.03). Also, CD4 <350 cells/mm³ (p = 0.01), viral load ≥1000 copies/mL (p = 0.01), WHO treatment stage II (T2) (p = 0.01), WHO treatment stage III (T3) (p = 0.01), adherence of poor (≤95%) (p = 0.01), hemoglobin <12 mg/dl (p = 0.01), current adherence of poor or ≤95% (p = 0.01), treatment duration of ≤24 months (p = 0.01), treatment duration of 25–72 months (p = 0.02), an initial regimen of AZT + 3TC + NVP (p = 0.04), current second-line regimen (p = 0.01), frequency of follow-up 1 month(p = 0.01), frequency of follow-up 2 months (p = 0.16), ambulatory patients (P = 0.01), single patients (p = 0.02), male patients (p = 0.01) (Table 4).

**Table 3** Baseline and Follow-Up Treatment-Related Characteristics of PLWHA in Jimma University Medical Center, 2019

| Variable | Category | Frequency n (%) |
|---|---|---|
| Duration of ART in months | 6–24 | 30 (9) |
| | 25–72 | 152 (45.8) |
| | Above 72 | 150 (45.2) |
| Current regimen | TDF + 3TC + EFV | 208 (62.7) |
| | DTG + 3TC + TDF | 19 (5.7) |
| | TDF + 3TC + NVP | 18 (5.4) |
| | AZT + 3TC + EFV | 18 (5.4) |
| | AZT +3TC + NVP | 56 (16.9) |
| | AZT + 3TC+ LPV/r | 4 (1.2) |
| | TDF + 3TC + LPV/r | 3 (0.9) |
| | TDF + 3TC + ATV/r | 6 (1.8) |
| Co-medications | Yes | 156 (43) |
| | No | 176 (53) |
| Ever switched regimens since starting treatment at this clinic | Yes | 65 (19.6) |
| | No | 267 (80.4) |
| Reason for switch | Suspected toxicity | 28 (8.4) |
| | Better first line available | 25 (7.5) |
| | Previous treatment failure | 9 (2.7) |
| | New TB | 3 (0.9) |
| Patients encountered suspected toxicity | D4T | 22 (6.6) |
| | AZT | 5 (1.5) |
| | NVP | 1 (0.3) |
| Adherence | Poor | 45 (13.6) |
| | Good | 287 (86.4) |
| Current Adherence | Poor | 38 (11.4) |
| | Good | 294 (88.6) |
| Lose to follow up | Yes | 0 (0) |
| | No | 332 (100) |

**Table 4** Bivariate Analysis of Associated Factors with Immunological Response of PLWHA, 2019 (n = 332)

| Variables | | Immunological Response | | Crude Estimates | | |
|---|---|---|---|---|---|---|
| | | $CD_4$>350 Cell/mm³ | $CD_4$<350 Cell/m³ | COR | (95% CI) | P |
| Health risk level alcohol use | No risk | 177 | 35 | 1 | | |
| | Low | 36 | 7 | 0.9 | 0.4–2.3 | 0.97 |
| | Moderate | 34 | 15 | 2.2 | 1.1–4.5 | 0.02* |
| | High | 14 | 14 | 5.0 | 2.2–11.5 | 0.01* |
| Health risk level | No risk | 243 | 61 | 1 | | |
| Cigarette use | Low | 17 | 6 | 1.4 | 0.5–3.7 | 0.49 |
| | Moderate | 1 | 3 | 11.9 | 1.2–116.8 | 0.03* |
| | High | 0 | 1 | | | 1 |
| Health risk level | No risk | 151 | 45 | 1 | | |
| Khat use | Low | 53 | 12 | 0.7 | 0.3–1.5 | 0.44 |
| | Moderate | 47 | 11 | 0.7 | 0.3–1.6 | 0.52 |
| | High | 10 | 3 | 1.0 | 0.2–3.8 | 0.99 |
| Sex | Male | 81 | 38 | 2.5 | 1.4–4.3 | 0.01* |
| | Female | 180 | 33 | 1 | | |
| Age (years) | ≤ 50 | 229 | 64 | 1 | | |
| | >50 | 32 | 7 | 0.78 | 0.3–1.9 | 0.57 |
| Marital status | Married | 139 | 35 | 1 | | |
| | Single | 33 | 18 | 2.1 | 1.0–4.2 | 0.02* |
| | Widowed | 29 | 6 | 0.8 | 0.3–2.1 | 0.68 |
| | Divorced | 60 | 12 | 0.7 | 0.3–1.6 | 0.53 |
| Functional status | Working | 251 | 58 | 1 | | |
| | Ambulatory | 10 | 13 | 5.6 | 2.3–13.4 | 0.01* |
| BMI | ≥18.5 | 216 | 59 | 1 | | |
| | < 18.5 | 45 | 12 | 0.98 | 0.5–1.9 | 0.9 |
| Follow-up frequency in months | 1 month | 51 | 31 | 6.4 | 1.8–22.9 | 0.01* |
| | 2 months | 128 | 29 | 2.4 | 0.6–8.4 | 0.16* |
| | 3 months | 50 | 8 | 1.7 | 0.4–6.9 | 0.45 |
| | 6 months | 32 | 3 | 1 | | |
| Co-morbidity | Yes | 56 | 12 | 1.3 | 0.7–2.7 | 0.4 |
| | No | 205 | 59 | 1 | | |
| Duration of treatment in months | ≤ 24 months | 18 | 12 | 4.0 | 1.7–9.7 | 0.01* |
| | 25–72 months | 114 | 38 | 2.0 | 1.1–3.6 | 0.02* |
| | >72 months | 129 | 21 | 1 | | |
| Initial regimen | TDF + 3TC + EFV | 149 | 50 | 1 | | |
| | TDF + 3TC + NVP | 14 | 4 | 0.8 | 0.2–2.7 | 0.78 |
| | AZT + 3TC + EFV | 14 | 2 | 0.4 | 0.1–1.9 | 0.27 |
| | AZT + 3TC + NVP | 64 | 10 | 0.4 | 0.2–0.9 | 0.04* |
| | D4T + 3TC + EVF | 11 | 2 | 0.5 | 0.1–2.5 | 0.43 |
| | D4T + 3TC + NVP | 7 | 3 | 1.2 | 0.3–5.1 | 0.73 |
| | ABC + 3TC + EVF | 2 | 0 | 0.0 | 0.0- | 0.99 |
| Current regimen class | Second line | 6 | 7 | 4.6 | 1.5–14.3 | 0.01* |
| | First-line | 255 | 64 | 1 | | |
| BaselineCD4 cell count | ≤350 cells/mm³ | 27 | 32 | 7.1 | 3.8–13.1 | 0.01* |
| | >350 cells/mm³ | 234 | 39 | 1 | | |
| Viral load | ≥1000 copies/mL | 7 | 28 | 23.6 | 9.7–57.4 | 0.01* |
| | < 1000 copies/mL | 254 | 43 | 1 | | |
| WHO treatment stage | I (T1) | 254 | 49 | 1 | | |
| | II (T2) | 15 | 17 | 5.6 | 2.6–12.1 | 0.01* |
| | III (T3) | 1 | 5 | 25.0 | 2.8–218.7 | 0.01* |

(*Continued*)

**Table 4** (Continued).

| Variables | | Immunological Response | | Crude Estimates | | |
|---|---|---|---|---|---|---|
| | | $CD_4$>350 Cell/mm³ | $CD_4$<350 Cell/m³ | COR | (95% CI) | P |
| Adherence | Poor (≤ 95%) | 22 | 23 | 5.2 | 2.6–10.0 | 0.01* |
| | Good (> 95%) | 239 | 48 | 1 | | |
| Hemoglobin level | < 12 mg/dl | 76 | 55 | 8.3 | 4.5–15.5 | 0.01* |
| | ≥ 12 | 185 | 16 | 1 | | |
| Current adherence | Poor (≤ 95%) | 14 | 24 | 9.0 | 4.3–18.6 | 0.01* |
| | Good (> 95%) | 247 | 47 | 1 | | |

**Notes**: Those variables with p-value < 0.25 under bivariate analysis were included in multivariate analysis. *Has a significant association.

**Table 5** Multivariable Logistic Regression Analysis of Associated Factors with the Immunological Response of HIV/AIDS Patients, 2019 (n = 332)

| Variables | | Immunological Response | | Adjusted Estimates | | |
|---|---|---|---|---|---|---|
| | | CD4>350 Cells/mm³ | $CD_4$<350 Cells/mm³ | AOR | (95% CI) | P |
| Health risk level alcohol use | No risk | 177 | 35 | 1 | | |
| | Low | 36 | 7 | 1.0 | 0.3–3.0 | 0.98 |
| | Moderate | 34 | 15 | 2.9 | 1.1–7.4 | 0.02* |
| | High | 14 | 14 | 4.3 | 1.2–14.8 | 0.02* |
| Baseline CD4 cell count | ≤ 350 cells/mm³ | 27 | 32 | 5.3 | 2.4–12.0 | 0.01* |
| | >350 cells/mm³ | 234 | 39 | 1 | | |
| Viral load | ≥1000 copies/mL | 7 | 28 | 9.2 | 3.2–26.6 | 0.01* |
| | < 1000 copies/mL | 254 | 43 | 1 | | |
| Current regimen class | Second line | 6 | 7 | 4.06 | 0.8–19.2 | 0.08 |
| | First-line | 255 | 64 | 1 | | |
| Hemoglobin level | < 12 mg/dl | 76 | 55 | 7.2 | 3.2–15.9 | 0.01* |
| | ≥ 12 mg/dl | 185 | 16 | 1 | | |
| Current adherence | Poor (≤ 95%) | 14 | 24 | 6.6 | 2.4–17.9 | 0.01* |
| | Good (> 95%) | 247 | 47 | 1 | | |

**Notes**: *Has significant association at p < 0.05, CI of 95%. Ref (reference).

In the multivariable logistic regression model (See Table 5), the inadequate immunological response was associated with high and moderate health risk level alcohol use (adjusted odds ratio (AOR) 4.3, 95% CI = 1.2–14.8) and (AOR 2.9, 95% CI = 1.0–7.4), respectively, CD4 <350 cells/mm³ (AOR 5.3, 95% CI = 2.4–12.0), viral load ≥1000 copies/mL (AOR 9.2, 95% CI = 3.2–26.6), hemoglobin level <12 mg/dl (AOR 7.2, 95% CI = 3.2–15.9) and current adherence of poor (≤95%) (AOR 6.6, 95% CI = 2.4–17.9). In the final model, moderate health risk level cigarette use, WHO treatment stage II, WHO treatment stage III, treatment duration of ≤24 months, treatment duration of 25–72 months, an initial regimen of AZT+3TC+NVP, current second-line regimen, frequency of follow-up 1 month, frequency of follow-up 2 months, ambulatory, single and male patients were not associated with inadequate immunological response.

## Discussion

Identifying and managing substance use is a challenge to a treatment program. Most treatment failure occurs due to the difficulty of delivering quality care. In this study, we found the extent of inadequate immunological response among PLWHA as 21.4% and an association of inadequate immunological response with moderate and high levels of health risk alcohol use.

The inadequate immunological response rate in this study (21.4%) is lower than in other studies with a modest comparative difference observed: a cohort of sub-Saharan Africa (27%),[2] in Oman Sultan Qaboos University Hospital (27%),[4] a study throughout Australia (28%).[3] In our study, the inadequate immunological response was a heterogeneous group of both viral-suppressed and unsuppressed immunological non-respondents. This should have made the proportion of inadequate immunological response higher. However, our result showed a lower percentage than from studies that exclude virally unsuppressed non-respondents. These may be due to the longer treatment duration that our participants had been on ART before entry to the current study (mean of 74 months) compared to the above studies in Australia, Omani, and sub-Saharan Africa. However, this finding is not comparable with a retrospective analysis conducted in Tanzania (50.25%) with a cutoff point of 350cells/mm$^3$.[5] This difference could be due to variations in socioeconomic class, the clinical status of clients, study design, and adequate patient care.

Substance use and inadequate immunological response are tied together. Alcohol-mediated effects on immune function occur through a combination of behavioral effects (adherence) and its direct effect on the immune system, which results in chronic inflammation, and effect on the liver, which affects drug metabolism through enzyme induction;-[19,20,24] this may lead to increased HIV disease progression.

In our study, the risk of inadequate immunological response in a moderate level of health risk alcohol users was around three times higher than those with no level of health risk. As in several previous studies, those with levels of health risk for alcohol use showed a high rate of inadequate immunological response than patients who are non-alcohol users.[19,21–23] However, a prospective study from America reported that for patients with baseline CD4 of >200 cells/mm³ moderate alcohol use does not affect the rate of decline of CD4+ cells to ≤200 cells compared to abstainers but for high-risk alcohol use does have. The discordance to the findings of 2010 Baum et al could be due to the difference in the definition of the outcome measure they used, a cut point of CD4 ≤200 cells to measure the association. Also, another significant difference was in contrast to our study patients included in Baum et al were those having baseline CD4 cells of >200 cells/mm³.[21]

In this sample of people living with HIV/AIDS in Jimma, a high level of health risk for alcohol use was associated with more than four times the odds of having inadequate immunological response compared to non-drinkers (no health risk level). This finding is supported by multiple studies[19,22] and similar to a finding of a prospective study from America that reported PLWHA with frequent alcohol use had a significantly inadequate immunological response 2.91 times more likely to present a decline of CD4 to ≤200 cells/mm³.[21] This result could have occurred because of consistent alcohol use findings among patients on ART in the study area, as showed in 2014 hazardous drinking, harmful drinking, and alcohol dependence were found in a significant number of patients in the study area.[29]

These findings imply that patients who present with alcohol use and $CD_4$ < 350 cells/mm³ need a much closer clinical follow-up to obtain a desirable immune recovery. Short-term interventions that aim to cut down alcohol use could be useful, but the high level of health risk alcohol users is more likely to be alcohol dependent and so require more extensive support. However, in this study, contrary to those who reported moderate and high health risk level alcohol use, those who reported low health risk level alcohol use did not have a significant association with inadequate immunological response compared to non-alcohol users (no health risk level).

In this study, levels of health risk for cigarette use had a significant association with inadequate immunological response in univariate analysis but were not found to have a significant association in the multivariate model. This is possibly due to the small number of samples in the cigarette use group. Levels of health risk for khat use did not have an association with inadequate immunological response. Previous studies on khat mostly focus on its association with nonadherence, but it has not been previously shown that khat use is not associated with worse HIV immunological response.

In our study, we found that poor current adherence was strongly associated with an inadequate immunological response where patients with poor current adherence were 6.646 times more likely to have inadequate immunological response than those with good current adherence. A retrospective follow-up study done in Tigray, Northern Ethiopia, also supported this finding, as clients with ≤95% adherence were 5.68 times more likely to have immunological failure compared to those having >95% adherence. This is mostly due to the indirect effect of poor adherence, which comes through an increase in HIV RNA replication.[12] Among the patients with inadequate immunological response, 36 (50.7%) of them are the levels of health risk for alcohol use. Ten percent of patients with levels of health risk alcohol use has poor adherence. Overall, it is likely that poor

adherence has played a role in the immunological response of patients with substance use problems but that may be a partial proxy for antiretroviral therapy adherence. We have not used a model to examine the potentially mediating effect of adherence. This may not enable us to show the independent effects of adherence and level of health risk alcohol use on inadequate immunological response.

Other factors that were significantly associated with inadequate immunological response, patients with baseline CD4 ≤350 cells/mm³ were more than five times more likely to have inadequate immunological response than patients who had CD4 >350 cells/mm³. A cohort study from Australia also supported this finding that 28% of patients with a CD4 cell count of <350 cells/μL showed an inadequate immunological response (CD4 cell <350 cells/μL) after 24 months of treatment.[3] The probable reason could be due to variation in the degree of immune suppression at treatment initiation or clinical status that patients with CD4 ≤350 cells/mm³ had.

It was also observed that patients with hemoglobin <12 mg/dl were significantly associated with inadequate immunological response. Hence, the odds of inadequate immunological response were increased more than seven times among patients with hemoglobin <12 mg/dl. A study by Kowalska et al[14] also reported that the recently measured hemoglobin level was significantly associated with disease progression than baseline hemoglobin measured at the start of treatment. This implies that the recently measured hemoglobin level could be useful in identifying patients with a higher risk of short-term disease progression; this is easily done in our setup because the BD FACSPresto™ machine also measures total hemoglobin concentration on the same sample and provides all the results concurrently. Maintaining optimal hemoglobin levels helps to prevent the development of AIDS-defining illnesses.

Patients with a viral load of ≥1000 copies/mL were more than nine times more likely to demonstrate inadequate immunological response compared to those <1000 copies/mL. This may be due to a shorter time interval in which the viral load was measured (within 3 months) or poor enrolment and current adherence, which a larger proportion of patients with viral load ≥1000 copies/mL had. In Gonder patients with viral load, ≥20 copies were 5 times more likely to have an immune failure.[13] A study in Ghana also supported this finding, patients with viral load ≥1000 copies/mL were 2 times more likely to have CD4 cells <350 cells/mm³. Besides, this finding is consistent with the scientific facts in that a higher HIV RNA results in more destruction of CD4 cells. Therefore, extra time may be needed with adherence support to obtain a CD4 cell count of >350cells/mm³.[6]

A causal inference between substance use and inadequate immunological response cannot be established in this study and it may be difficult to generalize the finding to a larger population because of the small sample size, single study area, and short-term follow-up period used. Also, this result cannot be generalized for severely ill patients who required emergency medical help. However, this study could imply the need for further longitudinal studies in Ethiopia to strengthen these findings and their clinical significance. Social desirability bias could be a limitation as persons who use alcohol and other substances tend to under-report or deny their use when interviewed, and we used the self-report of adherence to antiretroviral therapy, which is likely to underestimate the level of non-adherence.

## Conclusion

Around a quarter of the participants were with an inadequate immunological response. Participants with a moderate and high level of health risk for alcohol use were independently associated with inadequate immunological response. In an area where alcohol is widely consumed, defining a pattern of responsible use and developing community-based interventions are valuable healthcare priorities to be included as a comprehensive care package for people living with HIV/AIDS.

## Abbreviations

AIDS, Acquired Immune Deficiency Syndrome; AOR, Adjusted Odds Ratio; ART, Antiretroviral Therapy; ASSIST, Alcohol Smoking and Substance Involvement Screening Test; BMI, Body Mass Index; CDC, Center for disease control and prevention; CI, Confidence Interval; HIV, Human Immune Deficiency Virus; JUMC, Jimma University Medical Center; Kg, Kilo Gram; OR, Odds Ratio; PLWHA, People Living With HIV AIDS; TB, Tuberculosis; WHO, World Health Organization.

## Procedures/Methods

All methods were carried out per relevant guidelines and regulations.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author.

## Ethical Approval and Consent to Participate

Ethical clearance was obtained from the Institutional Review Board of the institute of health, Jimma University with a Reference Number of (IHRPGD/673/2019). All participants voluntarily participated in our study and signed informed consent forms before enrollment in the study. To keep confidentiality, all data were kept anonymously in the interview questionnaire. Privacy and confidentiality were ensured during patient interviews and the review of patient charts. All methods were carried out per relevant guidelines, regulations, and the declaration of Helsinki.

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## Author Contributions

All authors made substantial contributions to the conceptualization and design, investigation, writing original draft, formal analysis, review & editing of the article, gave final approval of the version to be published, and agreed to be accountable for all of the work.

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## Disclosure

The authors declare that they have no competing interests.

## References

1. HIV.gov. Other health issues of special concern for people living with HIV. HIV.gov; 2022. Available from: https://www.hiv.gov/hiv-basics/sta.
2. Kroeze S, Ondoa P. Suboptimal immune recovery during antiretroviral therapy with sustained HIV suppression in sub-Saharan Africa. *AIDS*. 2018;32:1043–1051. doi:10.1097/QAD.0000000000001801PMID:29547445
3. Falster K, Petoumenos K, Chuah J, et al. Poor baseline immune function predicts an incomplete immune response to combination antiretroviral treatment despite sustained viral suppression. *J Acquir Immune Defic Syndr*. 2010;50(3):307–313. doi:10.1097/QAI.0b013e3181945ed4
4. Ali ZG, Factors M-RB. Associated with immune discordant responses in treated HIV-infected abstract. *Open AIDS J*. 2019;13:25–30. doi:10.2174/1874613601913010025
5. Gunda DW, Kilonzo SB, Kamugisha E, Rauya EZ, Mpondo BC. Prevalence and risk factors of poor immune recovery among adult HIV patients attending care and treatment center in northwestern Tanzania following the use of highly active antiretroviral therapy: a retrospective study. *BMC Res Notes*. 2017;10(197):1–6. doi:10.1186/s13104-017-2521-0
6. Obiri-Yeboah D, Pappoe F, Baidoo I, et al. Immunologic and virological response to ART among HIV infected individuals at a tertiary hospital in Ghana. *BMC Infect Dis*. 2018;18(230):1–7. doi:10.1186/s12879-018-3142-5
7. Geng EH, Neilands TB. CD4 1 T cell recovery during suppression of HIV replication: an international comparison of the immunological efficacy of antiretroviral therapy in North America, Asia, and Africa. *Int J Epidemiol*. 2015;44:251–263. doi:10.1093/ije/dyu271
8. Tetrault JM, Fiellin DA, Sullivan LE. Substance Abuse and HIV: treatment Challenges By. *AIDS*. 2010;24:1–8. doi:10.1097/QAD.0b013e328333acfb
9. Azar MM, Springer SA, Meyer JP, Altice FL. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. *Drug Alcohol Depend*. 2011;112(3):178–193. doi:10.1016/j.drugalcdep.2010.06.014
10. Ogedengbe OO. Antiretroviral therapy and alcohol interactions: x-raying testicular and seminal parameters under the HAART Era. *Eur J Drug Metab Pharmacokinet*. 2017;43:121–125.
11. Kelley CF, Kitchen CMR, Hunt E. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clin Infect Dis*. 2009;94110(48):787–794. doi:10.1086/597093
12. Hailu GG, Hagos DG, Hagos AK. Virological and immunological failure of HAART and associated risk factors among adults and adolescents in the Tigray region of Northern Ethiopia. *PLoS One*. 2018;30(5):1–17. doi:10.1371/journal.pone.0196259

13. Ayele G, Tessema B, Amsalu A, Ferede G, Yismaw G. Prevalence and associated factors of treatment failure among HIV / AIDS patients on HAART attending University of Gondar Referral Hospital Northwest Ethiopia. *BMC Immunol*. 2018;19(37):1–13. doi:10.1186/s12865-018-0278-4
14. Kowalska J, Mocroft A, Blaxhult A, et al. Current hemoglobin levels are more predictive of disease progression than hemoglobin measured at baseline in patients receiving antiretroviral treatment for HIV type 1 infection. *AIDS Res Hum Retroviruses*. 2007;23(10):1183–1188. doi:10.1089/aid.2006.0292
15. Adam Gonzalez MJ, Mimiaga JI, Andres Bedoya SAS, Andres Bedoya C, Safren SA. Substance use predictors of poor medication adherence: the role of substance use coping among HIV-infected patients in opioid dependence treatment. *AIDS Behav*. 2014;17(1):168–173. doi:10.1007/s10461-012-0319-6
16. Macmadu A, Reddon H, Brandon DL, et al. Crack cocaine use frequency is associated with HIV disease severity independent of antiretroviral therapy exposure_ a prospective cohort study. *AIDS Behav*. 2022;26(10):3356–3364. doi:10.1007/s10461-022-03648-y
17. Liang J, Nosova E, Reddon H, et al. Longitudinal patterns of illicit drug use, antiretroviral therapy exposure and plasma HIV-1 RNA viral load among HIV-positive people who use illicit drugs. *AIDS*. 2021;34(9):1389–1396. doi:10.1097/QAD.0000000000002551
18. Eugenia Socías M. Substance use and adherence to antiretroviral therapy: what is known, and what is unknown. *Curr Infect Dis Rep*. 2019;20(9):1–10.
19. Miguez MJ, Shor-posner G, Morales G, Rodriguez A, Burbano X. Research article HIV treatment in drug abusers: impact of alcohol use. *Addict Biol*. 2003;8:33–37. doi:10.1080/1355621031000069855
20. Bagby GJ, Nelson S. Alcohol's s role in HIV transmission and disease progression. *Alcohol Res Heal*. 2010;33(3):207.
21. Baum MK, Rafie C, Lai S, Sales S, Page JB, Campa A. Alcohol use accelerates HIV disease progression. *AIDS Res Hum Retroviruses*. 2010;26(5):511–518. doi:10.1089/aid.2009.0211
22. Malbergier A, Abrantes R, Donola L. Alcohol dependence and CD4 cell count: is there a relationship? *AIDS Care*. 2015;27(1):54–58. doi:10.1080/09540121.2014.947235
23. Joshi KS, Chavan G. Alcohol: is it detrimental to HIV infected individuals on antiretroviral therapy? *Int J Res Med Sci*. 2016;4(8):3146–3152. doi:10.18203/2320-6012.ijrms20162216
24. Brandon DL, Marshall JP, Tate KA, et al. Long-term alcohol use patterns and HIV disease severity. *AIDS*. 2018;31(9):1313–1321.
25. Conen A, Fehr J, Glass TR, Furrer H, Weber R, Vernazza P. Self-reported alcohol consumption and its association with adherence and outcome of antiretroviral therapy in the Swiss HIV Cohort Study. *Int Med Press*. 2009;14(3):349–357.
26. Moss C, Mendoza-sassi RA, Dias L, Nader MM, Maria A, De MB. Alcohol use disorders among people living with HIV / AIDS in Southern Brazil: prevalence, risk factors, and biological markers outcomes. *BMC Infect Dis*. 2017;17(263):1–8. doi:10.1186/s12879-017-2374-0
27. Magidson JF, Fatch R, Orrell C, Amanyire G, Haberer JE, Hahn JA. Biomarker - measured unhealthy alcohol use in relation to CD4 count among individuals starting ART in Sub - Saharan Africa. *AIDS Behav*. 2018;018(0123456789):2364. doi:10.1007/s10461-018-2364-2
28. Segni MT, Teshome G, Demissie HF. Substance use and associated factors among retro viral infected (RVI) patients on antiretroviral treatment (ART) at assela teaching hospital. *J AIDS Clin Res*. 2017;8(6):6–10.
29. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Alcohol use disorders and associated factors among people living with HIV who are attending services in southwest Ethiopia. *Biomedcentral*. 2014;7(828):1–9.
30. Ande A, McArthur C, Anil Kumar SK. Tobacco smoking effect on HIV-1 pathogenesis: role of cytochrome P450 isozymes. *Expert Opin Drug Metab Toxicol*. 2014;9(11):1453–1464. doi:10.1517/17425255.2013.816285
31. Hile SJ, Feldman MB, Alexy ER, Irvine MK. Recent tobacco smoking is associated with poor HIV medical outcomes among HIV-infected individuals in New York. *AIDS Behav*. 2016;20(8):1722–1729. doi:10.1007/s10461-015-1273-x
32. Waweru P, Anderson R, Venter WDF, et al. The prevalence of smoking and the knowledge of smoking hazards and smoking cessation strategies among HIV positive patients in Johannesburg, South Africa. *S Afr Med J*. 2014;103(11):858–860. doi:10.7196/SAMJ.7388
33. Theresa Winhusen DJ, Feaster RD. Baseline cigarette smoking status as a predictor of virologic suppression and CD4 Cell count during one - year follow - up in substance users with uncontrolled HIV infection. *AIDS Behav*. 2017;17(1928):1–7. doi:10.1007/s10461-017-1928-x
34. Brown JL, Winhusen T, Ralph J, et al. The Association between cigarette smoking, virologic suppression, and CD4+ lymphocyte count in HIV-infected Russian women. *AIDS Care*. 2018;29(9):1102–1106. doi:10.1080/09540121.2017.1327645
35. Conrad Kabali DM, Cheng DB, Bridden C, Horsburgh R, Horsburgh CR, Samet JH. Recent cigarette smoking and HIV disease progression: no evidence of an association. *AIDS Care*. 2012;23(8):947–956. doi:10.1080/09540121.2010.542128
36. Lifson AR, Workneh S, Shenie T, et al. Prevalence and factors associated with use of khat: a survey of patients entering HIV treatment programs in Ethiopia. *Addict Sci Clin Pract*. 2017;12(3):1–7. doi:10.1186/s13722-016-0069-2
37. Soboka M, Tesfaye M, Feyissa GT, Hanlon C. Khat use in people living with HIV: a facility-based cross-sectional survey from South West Ethiopia. *BMC Psychiatry*. 2015;15(69):1–7. doi:10.1186/s12888-015-0446-5
38. Only SE Who - assist v3.0; 2019. Available from: https://www.who.int/substance_abuse/activities/assist_test/en/access. Accessed November 21, 2022.
39. Jennifer McNeely SM, Strauss SW, Wright S, et al. Journal of substance abuse treatment test-retest reliability of a self-administered Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) in primary care patients. *J Subst Abuse Treat*. 2014;47(1):93–101. doi:10.1016/j.jsat.2014.01.007
40. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016; Available from: http://www.who.int/hiv/pub/guidelines/arv2016/download/en. Accessed January 8, 2019.
41. ART guidelines for HIV-Infected Adults and Adolescents. National AIDS control organization ministry of health and family Welfare Government of India; 2013.
42. World Health Organization HIV/AIDS Programme. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommendations for public health approach; 2013. Available from: www.who.int. Accessed November 21, 2022.
43. Gesesew HA, Ward P, Kifle Woldemichael LM. Immunological failure in HIV-infected adults from 2003 to 2015 in Southwest Ethiopia: a retrospective cohort study. *BMJ Open*. 2018;4(8):1–10.