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Original Research

Antiretroviral adherence and treatment outcomes among patients living with HIV at an Indonesian HIV clinic: a cross-sectional study

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Abstract

Objective: This study assessed antiretroviral adherence and treatment outcomes among outpatients with human immunodeficiency virus (HIV). Methods: A cross-sectional study was performed on patients with HIV over 18 years old receiving antiretroviral therapy for at least six months at an Indonesian clinic, from January to March 2021. The previously validated self-reported adherence questionnaire was used to recall antiretroviral use. Viral load and CD4 were indicators of treatment outcomes. Binary logistic regression was used to explore factors associated with nonadherence and poor treatment outcomes. Results: Ninety-five patients were included in the study (male 70.5%, median [interquartile range, IQR] age 35 [29–42] years, and median [IQR] treatment duration 29 [15–49] months). Adherence greater than 95% was observed in 89.5%, 88.4%, 95.8% of the patients in the past week, month, and three months, respectively. Patients with secondary education or lower were associated with low adherence (adjusted odds ratio, aOR: 7.73, 95%CI: 1.12–53.19). Viral suppression and improved CD4 were observed in 83.2% and 68.4% of the patients, respectively. Taking non-nucleoside reverse transcriptase inhibitors (NNRTIs)-based regimen was associated with viral suppression (aOR: 0.01, 95%CI: 0.00–0.14) as well as high CD4 count (aOR: 0.16, 95%CI: 0.03–0.83). Being diagnosed with stage 4 of HIV (aOR: 72.38, 95%CI: 3.11–1687.28) and having adherence of 95% or lower (aOR: 68.84, 95%CI: 4.86–974.89) were associated with non-suppressed viral load, and having HIV stage 3 (aOR: 7.81, 95%CI: 1.26–48.40) or 4 (aOR: 26.15, 95%CI: 3.42–200.10) at diagnosis was associated with low CD4. Conclusion: Rates of self-reported adherence and treatment outcomes were high. Secondary education or lower was a predictor of low adherence. Using NNRTIs-based therapy was associated with good treatment outcomes; meanwhile, stage 3 or 4 of HIV at diagnosis and low adherence were predictors of poor outcomes. Therefore, strategies to improve adherence and treatment outcomes are warranted.

Keywords: antiretroviral agents; CD4 count; HIV; Indonesia; medication adherence; viral load

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INTRODUCTION

In 2020, globally an estimated 37.7 million people were living with human immunodeficiency virus (HIV) and 1.5 million became newly infected with HIV.[1] Indonesia is one of few countries with an increasing number of new HIV infections, with a cumulative number of HIV cases reported from the year 2005 to December 2020 of 419,551.[2] East Java ranked the second highest province in Indonesia that reported around sixty-five thousand people being infected with HIV, and most of them resided in Surabaya.[2] Despite the implementation of a test-and-treat policy for newly diagnosed patients and increased antiretroviral therapy (ART) coverage in this region, the annual HIV-related mortality is still rising.[2] Possible causes include poor adherence to ART and treatment failure.

A meta-analysis of 43 studies worldwide in 2015 reported that the mean rate of adults with HIV reporting optimal adherence was 63.4%, and among patients with suboptimal ART adherence, 46.8% of them had virologic failure.[3] In Indonesia, among 142,906 patients with HIV who were receiving ART by the end of 2020, only 33,027 (23.1%) of them were virologically suppressed.[2] Patient, disease, and medication-related factors have been reported to associate with adherence and virological suppression in ART.[4–10] However, predictors to treatment outcomes differ across settings and population groups. Meta-analysis data showed that even though optimal adherence was associated with a lower risk of virologic failure, more

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patients with optimal adherence experienced virologic failure in developing countries than in developed countries.[3] Another meta-analysis revealed that virological failure was 6-fold higher among patients showing poor ART adherence than those with good adherence and 5-times higher among patients with CD4 <200 cells/mm^3 than those with higher CD4 in resource-limited settings.[6]

Given the insufficient number of patients on ART and sub-optimal viral suppression in Indonesia, evaluating medication adherence and clinical efficacy of ART is necessary to help health care providers, including pharmacists, develop strategies to improve HIV treatment and care. Therefore, this study aimed to assess adherence to ART and treatment outcomes among patients with HIV and to identify the contributing factors.

METHODS

Study design and participants

A cross-sectional study was conducted among outpatients with HIV being treated at the HIV clinic of a university hospital in Surabaya, Indonesia, between January to March 2021. The clinic is run by multidisciplinary professionals including internists, pulmonologists, dermatologists, nurses, midwives, and pharmacists who have been trained by the Indonesian Ministry of Health to provide HIV care and treatment. Patients usually visit the clinic once every month or two months to access their ART.

The study sample size was calculated based on a single population proportion formula[11] by considering the proportion of 40% reporting poor adherence with a 95% confidence interval and a 10% margin of error, thus the minimum sample size was 92. Inclusion criteria for the study were patients with HIV who were aged 18 years and older and receiving first line ARTs for at least six months. HIV diagnosis was confirmed by the positive or reactive results either from antibody tests, three-consecutive HIV-1 antigen/antibody tests, or nucleic acid tests performed at the clinic or other trusted clinical laboratory. ART referred to a combination of antiretroviral drugs for treating HIV infection, according to the national guideline-recommended regimens and consisting of at least two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI) supplied for at least a 30-day period. A random sampling method was used to achieve sample size; the study investigators approached eligible patients visiting the clinic individually, informed of the purpose and procedures of the study, and recruited those who volunteered to participate. They were requested to provide written informed consent if they agreed to enrol in the study. There were no exclusion criteria; however, their data were removed from the analysis if they withdrew the consent after enrolment. The study participants did not receive any financial compensation.

The study protocol was reviewed and approved by the ethics research committee at Universitas Airlangga Hospital in Surabaya, Indonesia (approval number: 131/KEP/2020 dated March 31, 2020). The procedures used in this study also adhered to the tenets of the Declaration of Helsinki.

Data collection

All participants' information were de-identified. Demographic information (sex, age, education level, HIV clinical stage at diagnosis based on the World Health Organization [WHO] classification, time since HIV diagnosis, other diseases) and recent treatment outcomes (HIV-1 RNA viral load, CD4 cell count) were collected from patients' medical records. Data on therapy (time since starting ART, current ART regimen, other medications) were retrieved from the clinic's pharmacy records. These records were obtained with the patients' permission. ART adherence was measured using the previously validated self-reported adherence (SERAD) questionnaire to recall ART use during the last week, the last month, and the last three months. The feasibility and validity of the SERAD questionnaire in measuring adherence in HIV-infected patients has been tested in a multicentre study.[12]

A forward-backward translation protocol to develop a Bahasa Indonesia version of the SERAD questionnaire (**Supplementary Text**) derived from the original English version was applied before the commencement of the study. Permission to use the SERAD questionnaire was granted by its original authors. The questionnaire is publicly available at www.flsida.org/serad in English and Spanish versions. The forward translation into Bahasa Indonesia was done by two English-speaking Indonesian translators. The outcomes were discussed in order to compare the two translations and reach an agreement. An English native speaker who understood the Bahasa Indonesia language (from the university language centre) then backward translated the Bahasa Indonesia version. The backward translation result and the original version were compared and discussed, and the Bahasa Indonesia version was ensured to have the same meaning and context as the original version. A pilot testing of the Bahasa Indonesia version was administered to 24 patients with HIV from the same clinic in April to June 2019 (ethic's approval number: 120/KEH/2019 dated March 26, 2019). The value of Cronbach's alpha coefficient for the Bahasa Indonesia version of SERAD questionnaire was 0.821 (>0.70) and the correlation coefficient (r-value >0.80) with p-value <0.05 met the criteria of reliability and construct validity (data not shown).

The SERAD questionnaire was designed as an interviewer-administered tool and most of the questions were open to obtain quantitative answers, and a usage guide was available to facilitate the administration by the researchers.[12] The first part of the questionnaire collected information on the medication prescribed, the schedule to be followed, the number of dosage units prescribed, and the number of daily doses. The second part assessed the adherence data based on the number of times the patient took the medication (percentage of adherence) during the past week, the past month, and the past three months, and the number of times the patient complied with the intake conditions (percentage of intake conditions respected) over the last week and the last month. The last month period also included the last week, so if the patient reported more missed

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doses during the last month, these included also the missed doses during the last week. The last part of the questionnaire calculated the percentages of adherence with regard to the missed doses and the times that intake conditions were not respected by the following formula: (total number of dosage units prescribed – total number of times reported) / (total number of dosage units prescribed) X 100.

Data analysis

Data were tabulated using Microsoft Excel (2016), coded, and checked for completeness. The dependent variables were adherence level, viral load, and CD4 cell count. Patients who reported taking >95% of their ART as prescribed were considered as "highly adherent", while patients with adherence 95% or lower were grouped into "less adherent".[12] The treatment outcomes, virological response (viral load) and immunological recovery (CD4 cell count), were categorized based on the target levels stated in the clinical guideline applicable at the study site. Viral load was classified as "suppression" (viral load <1,000 copies/ml) or "non-suppression" (viral load ≥1,000 copies/ml), while CD4 cell count was grouped into "low" (CD4 <200 cells/mm^3) or "high" (CD4 ≥200 cells/mm^3).[13] The independent variables included age, sex, education level, HIV clinical stage at diagnosis, time since HIV diagnosis, duration of ART, type of ART regimen, and number of tablets taken daily. The adherence level was also considered as a predictor when analysing the treatment outcomes.

Descriptive statistics were used to describe patients' characteristics, levels of adherence, and the prevalence of treatment outcomes. The Kolmogorov-Smirnov test and a Q-Q plot were used to assess whether the continuous variables had a normal distribution. Data are presented in frequencies, percentages, and medians (interquartile ranges, IQRs). Reasons for non-adherence are displayed as bar charts.

Binary logistic regression was performed to explore predictive factors associated with the likelihood of being less adherent to ART, having non-suppressed viral load, and having low CD4. The assumptions underlying logistic regression model for continuous variables were previously tested; the Box-Tidwell test and a scatter plot were used to check the linearity to the logit of the outcomes, while collinearity diagnostics were used to test the absence of multicollinearity or correlations between variables. Finally, the strength of the association was presented as odds ratio (OR) with a 95% confidence interval (CI).

Covariates for the final model were selected using a backward elimination with the alpha level of 0.05, and the final models retained variables with *p*-value <0.25. The model's performance was evaluated with regard to its calibration and discrimination. The Hosmer and Lemeshow "goodness-of-fit" test was used to assess the model's calibration (a model with *p*-value of the test >0.05 is a good fit), while the C statistic, area under the receiver operating characteristic curve, was used to examine its discrimination (a model with area under the curve closer to 1 has a better performance at distinguishing between positive and negative outcomes). Variables with *p*-value <0.05 at the final models were considered statistically significant. All statistical analyses were performed using SPSS® Statistics v. 28.0 for Windows (IBM Corp, Armonk, New York). The reporting of this study conforms to STROBE guidelines.[14]

RESULTS

Patient characteristics

One hundred and six patients receiving ART were approached during the study period, 95 of them provided written consent and were included in the study. None of them withdrew participation after enrolment. The characteristics of the patients are shown in Table 1. The median (IQR) age was 35

Table 1. Patient characteristics (N=95)

Variable	n (%)
Age (years)	
Median (IQR)	35 (29–42)
Range (min, max)	21–76
Sex	
Female	28 (29.5)
Male	67 (70.5)
Education level	
College/university	44 (46.3)
High school or lower	51 (53.7)
WHO HIV clinical stage at diagnosis	
1	30 (31.6)
2	25 (26.3)
3	25 (26.3)
4	15 (15.8)
Time since HIV diagnosis (months)	
Median (IQR)	33 (16–53)
Range (min, max)	6–158
Other diseases	
Heart diseases	2 (2.1)
Diabetes mellitus	1 (1.0)
Upper respiratory infection	1 (1.0)
Sexually transmitted infection	1 (1.0)
Duration of ART (months)	
Median (IQR)	29 (15–49)
Range (min, max)	6–109
Type of ART regimen	
NNRTIs-based	78 (82.1)
INSTIs-based	10 (10.5)
PIs-based	2 (2.1)
Triple NRTIs	5 (5.3)
Other medications	
Antimicrobial agents[a]	15 (15.8)
Analgesics	6 (6.3)

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Table 1. Patient characteristics (N=95)	
Variable	**n (%)**
Antihypertensive agents	4 (4.2)
Antidiabetic drugs	2 (2.1)
Antihistamines	2 (2.1)
Mucolytics	2 (2.1)
Lipid lowering agents	1 (1.0)
Number of tablets taken daily	
Median (IQR)	1 (1–4)
Range (min, max)	1–10

Note: [a] Including cotrimoxazole prophylaxis used by patients at HIV clinical stage 3 or 4 or CD4 cell count ≤200 cells/mm^3

ART=antiretroviral therapy; HIV=human immunodeficiency virus; INSTI=integrase strand transfer inhibitor; IQR=interquartile range; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside/nucleotide reverse transcriptase inhibitor; PI=protease inhibitor; WHO=World Health Organization

(29–42) years, and sixty-seven patients (70.5%) were male. Forty patients (42.1%) were in clinical stage 3 or 4 of HIV at diagnosis. The median (IQR) duration of HIV infection was 33 (16–53) months, while the median (IQR) length of ART use was 29 (15–49) months.

Adherence to ART

ART adherence of >95% (highly adherent) was observed in 85 (89.5%), 84 (88.4%), and 91 (95.8%) patients in the past week, past month, and past three months, respectively, as shown in Table 2. More patients (84.2%) were highly adherent to the intake conditions during the last month compared to those (75.8%) in the last week. Reasons for failing to take the medications can be seen in Supplementary Figure S1. Forgetfulness was the most common reason reported for missing ART doses in the last week and last month, while being asleep was the most cited reason in the last three months. Furthermore, simply forgetting was the most prevalent reported reason for not respecting intake conditions during the last week and the last month (Supplementary Figure S2).

The results of the bivariate analysis for variables associated with low ART adherence are shown in Supplementary Table S1. In the multivariable analysis (**Table 3**), having a secondary or lower education level increased the probability that a patient was less adherent to ART in the past month by 7.7 times (adjusted OR [aOR]: 7.73, 95%CI: 1.12–53.19). Furthermore, it

Table 2. Prevalence of adherence and intake conditions respected according to the self-reported adherence (N=95)			
Measure	**n (%) per period**		
	Last week	**Last month**	**Last three months**
Adherence to ART			
Range (min, max)	57.1–100.0%	86.6–100.0%	94.4–100.0%
Highly adherent	85 (89.5)	84 (88.4)	91 (95.8)
Less adherent	10 (10.5)	11 (11.6)	4 (4.2)
Intake conditions respected			
Range (min, max)	28.6–100.0%	83.3–100.0%	N/A[a]
Highly adherent	72 (75.8)	80 (84.2)	N/A
Less adherent	23 (24.2)	15 (15.8)	N/A

Note: [a] The number of times the patient complied with the intake conditions (percentage of intake conditions respected) over the last three months was not assessed in the self-reported adherence questionnaire.
ART=antiretroviral therapy; N/A=not applicable

Table 3. Factors associated with low adherence to antiretroviral therapy among outpatients with HIV

Variable	**Adherence to ART, n (%)**		**OR (95%CI)**	**adjusted OR (95%CI)**	***p*-value**
	Less adherent[a] (N=11)	**Highly adherent (N=84)**			
Age (years) Median (IQR)	30.0 (28.0–35.0)	35.0 (29.3–42.8)	0.93 (0.86–1.01)	0.88 (0.77–1.01)	0.08
Sex					
Female	4 (36.4)	24 (28.6)	1.00	1.00	
Male	7 (63.6)	60 (71.4)	0.70 (0.19–2.61)	0.13 (0.01–1.29)	0.08
Education level					
College/ university	2 (18.2)	42 (50.0)	1.00	1.00	
High school or lower	9 (81.8)	42 (50.0)	4.50 (0.92–22.08)	7.73 (1.12–53.19)	0.04*
WHO HIV clinical stage at diagnosis					
1	4 (36.4)	26 (31.0)	1.00	1.00	
2	1 (9.1)	24 (28.6)	0.27 (0.03–2.60)	0.67 (0.05–9.34)	0.76
3	4 (36.4)	21 (25.0)	1.24 (0.28–5.55)	6.26 (0.58–67.71)	0.13
4	2 (18.2)	13 (15.5)	1.00 (0.16–6.19)	11.16 (0.57–218.70)	0.11
Time since HIV diagnosis (months) Median (IQR)	21.0 (9.0–43.0)	35.0 (16.3–55.3)	0.98 (0.95–1.01)	0.98 (0.94–1.02)	0.24
Number of tablets taken daily Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–4.0)	0.62 (0.35–1.13)	0.55 (0.26–1.15)	0.11

Notes: The results of the Hosmer and Lemeshow "goodness-of-fit" test of the final model showed that χ^2=1.36, degrees of freedom=8, and *p*=0.99. The area under the receiver operating characteristic curve of the model was 0.86 (95%CI: 0.78–0.94).
[a] Less adherent was defined by having an adherence of 95% and lower with regard to the doses missed in the last month.
*Statistically significant at *p*-value <0.05.
ART=antiretroviral therapy; CI=confidence interval; HIV=human immunodeficiency virus; OR=odds ratio; WHO=World Health Organization

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was found that in the past three months there were 91 (95.8%) patients showing an adherence higher than 95% and 4 (4.2%) patients had an adherence level of 94.4%. This would lead to poor statistics for a particular subgroup (i.e., less adherent), and thus factors contributing adherence in the last three months were not studied further.

Treatment outcomes

Viral suppression and improved (high) CD4 cell count were observed in 79 (83.2%) and 65 (68.5%) patients, respectively. The bivariate analysis of variables associated with non-suppressed viral load can be seen in Supplementary Table S2. The final multivariable model (Table 4) shows that an increased odds of having viral non-suppression was associated with patients being diagnosed with the last stage of HIV (aOR: 72.38, 95%CI: 3.11–1687.28) as well as patients being less adherent to ART in the past month (aOR: 68.84, 95%CI: 4.86–974.89). In contrast, a viral suppression was associated with using non-nucleoside reverse transcriptase inhibitors (NNRTIs)-based ART regimen (aOR: 0.01, 95%CI: 0.00–0.14).

Furthermore, the results of bivariate analysis for variables associated with low CD4 count are shown in Supplementary Table S3. In the final multivariable model (Table 5), whereas patients being diagnosed with HIV stage 3 (aOR: 7.81, 95%CI: 1.26–48.40) or 4 (aOR: 26.15, 95%CI: 3.42–200.10) were more likely to have CD4 <200 cells/mm^3, those who were taking NNRTIs-based ART were associated with a high CD4 cell count (aOR: 0.16, 95%CI: 0.03–0.83).

Table 4. Factors associated with non-suppressed viral load among patients with HIV at an Indonesian clinic

Variable	Viral load, n (%)		OR (95%CI)	adjusted OR (95%CI)	*p*-value
	Non-suppression[a] (N=16)	Suppression (N=79)			
WHO HIV clinical stage at diagnosis					
1	1 (6.3)	29 (36.7)	1.00	1.00	
2	2 (12.5)	23 (29.1)	2.52 (0.22–29.58)	2.98 (0.16–55.43)	0.46
3	6 (37.5)	19 (24.1)	9.16 (1.02–82.21)	5.77 (0.46–72.74)	0.18
4	7 (43.8)	8 (10.1)	25.38 (2.71–237.57)	72.38 (3.11–1687.28)	0.008*
Type of ART regimen					
INSTIs-based	6 (37.5)	4 (5.1)	1.00	1.00	
NNRTIs-based	7 (43.8)	71 (89.9)	0.07 (0.02–0.29)	0.01 (0.00–0.14)	<0.001*
PIs-based	2 (12.5)	0	N/A	N/A	1.00
Triple NRTIs	1 (6.3)	4 (5.1)	0.17 (0.01–2.09)	0.11 (0.00–3.04)	0.19
Last month adherence					
Highly adherent	11 (68.8)	73 (92.4)	1.00	1.00	
Less adherent	5 (31.3)	6 (7.6)	5.53 (1.44–21.24)	68.84 (4.86–974.89)	0.002*

Notes: The results of the Hosmer and Lemeshow "goodness-of-fit" test of the final model showed that χ^2=16.13, degrees of freedom=5, and *p*=0.006. The area under the receiver operating characteristic curve of the model was 0.93 (95%CI: 0.82–1.00).
[a] Viral load non-suppression was defined as having a viral load of 1,000 copies/ml and higher.
*Statistically significant at *p*-value <0.05.
ART=antiretroviral therapy; CI=confidence interval; HIV=human immunodeficiency virus; INSTI=integrase strand transfer inhibitor; N/A=not available; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside/nucleotide reverse transcriptase inhibitor; OR=odds ratio; PI=protease inhibitor; WHO=World Health Organization

Table 5. Factors associated with low CD4 cell count among patients with HIV at an Indonesian clinic

Variable	CD4 cell count, n (%)		OR (95%CI)	adjusted OR (95%CI)	*p*-value
	Low[a] (N=30)	High (N=65)			
Sex					
Female	4 (13.3)	24 (36.9)	1.00	1.00	
Male	26 (86.7)	41 (63.1)	3.81 (1.18–12.22)	4.32 (0.98–19.09)	0.05
WHO HIV clinical stage at diagnosis					
1	2 (6.7)	28 (43.1)	1.00	1.00	
2	7 (23.3)	18 (27.7)	5.44 (1.02–29.19)	5.30 (0.85–33.11)	0.08
3	11 (36.7)	14 (21.5)	11.00 (2.14–56.57)	7.81 (1.26–48.40)	0.03*
4	10 (33.3)	5 (7.7)	28.00 (4.67–168.00)	26.15 (3.42–200.10)	0.002*

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Type of ART regimen					
INSTIs-based	6 (20.0)	4 (6.2)	1.00	1.00	
NNRTIs-based	19 (63.3)	59 (90.8)	0.22 (0.06–0.84)	0.16 (0.03–0.83)	0.03*
PIs-based	2 (6.7)	0	N/A	N/A	1.00
Triple NRTIs	3 (10.0)	2 (3.1)	1.00 (0.11–8.95)	3.74 (0.20–68.57)	0.37
Last month adherence					
Highly adherent	25 (83.3)	59 (90.8)	1.00	1.00	
Less adherent	5 (16.7)	6 (9.2)	1.97 (0.55–7.04)	4.19 (0.75–23.41)	0.10

Notes: The results of the Hosmer and Lemeshow "goodness-of-fit" test of the final model showed that χ^2=3.54, degrees of freedom=6, and p=0.74. The area under the receiver operating characteristic curve of the model was 0.82 (95%CI: 0.73–0.91).
[a] Low CD4 cell count was defined by having CD4 less than 200 cells/mm^3.
*Statistically significant at p-value <0.05.
ART=antiretroviral therapy; CI=confidence interval; HIV=human immunodeficiency virus; INSTI=integrase strand transfer inhibitor; N/A=not available; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside/nucleotide reverse transcriptase inhibitor; OR=odds ratio; PI=protease inhibitor; WHO=World Health Organization

DISCUSSION

This study provides evidence on medication adherence and treatment outcomes among patients living with HIV and receiving first line ART at an Indonesian HIV clinic. The majority of patients had a high ART adherence, viral suppression, and improved CD4. Social, medication, and disease-related factors were identified to contribute to the ART adherence and treatment outcomes.

The study showed that patients with a secondary education level or lower were associated with low ART adherence over the last month compared to those with college or university degrees, and a similar finding has been reported in previous studies.[15,16] Better education and literacy may facilitate communication with health care providers and increase retention of information provided, thereby enhancing adherence to ART.[15] Literate patients may have a greater understanding of ART efficacy and take their medicines correctly to maintain therapeutic effect.[17]

The most common reasons reported for missing ART doses in this study were forgetfulness and falling asleep. In addition, forgetfulness was the most common reason reported for not respecting intake conditions. Forgetfulness and sleeping through dosing time have been reported as barriers to adherence regardless of adherence level or viral load and increased the odds of having a treatment interruption and detectable viral load among patients.[18,19] Furthermore, more patients in the present study were highly adherent to the intake conditions during the last month compared to those in the last week, and this might be due to the memory effect in the self-reported measure. Therefore, further strategies incorporating reminder to improve treatment adherence should be implemented.

Patients who were receiving NNRTIs-based ART regimen were more likely to have good treatment outcomes compared to those taking integrase strand transfer inhibitors (INSTIs)-based regimen. This finding is in contrast to a previous report that a proportion of patients treated with an NNRTI-based regimen suffered from virologic failure.[20] This implies that even though NNRTIs-based regimens are supplied in multiple tablets (e.g., a combination of tenofovir, lamivudine, and nevirapine, or zidovudine, lamivudine and efavirenz), they are generally tolerated for patients at the study site. Furthermore, a once-daily single-tablet INSTI-based regimen containing dolutegravir was introduced in mid/late 2020 to patients who were newly diagnosed or did not tolerate to an NNRTI-based regimen. Thus, the outcome of this new regimen could not be fully seen during the study period.

Patients with HIV stage 4 at diagnosis as well as those who had poor adherence to ART were likely to develop virological failure. Patients might be unaware of their HIV status until later stages of infection resulting in uncontrolled viral replication and poor immune system.[4,6,9] Thus, early screening for people who are at risk of HIV infection is needed. Furthermore, virological failure was prevalent among patients with poor ART adherence.[4,6] Poor adherence may result in suboptimal drug concentration and the loss of ART therapeutic effect in the inhibition of viral replication, which in turn leads to accelerated disease progression, HIV transmission, development of drug resistance, and premature death.[21] The reinforcement of medication adherence counselling by pharmacists, for instance, during the life course of taking ART is therefore needed. Patients on first-line ART drugs who are at risk of immunological and virological failure could immediately benefit from early detection, adherence support, repeat viral load testing, and switching to a second-line ART regimen.[9]

The present study also showed that patients diagnosed with advanced HIV disease (stage 3 or 4) were at risk in developing immunological failure. Having baseline CD4 counts <200 cells/mm^3 and being on tuberculosis treatment, as commonly found in patients with HIV stage 3 or 4, has been reported to be associated with poor treatment outcomes.[8,22,23] Patients with advanced HIV disease have a poor immune system and are more prone to severe illnesses (e.g., tuberculosis or other viral infections) and death. Therefore, all HIV-infected patients should start ART immediately irrespective of their clinical stages to lower the risk of disease progression.[13,22]

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Nevertheless, the study has some limitations and thus the results should be interpreted with caution. It was conducted in a single centre and prone to selection bias. Only patients who actively went to the clinic participated to the study, while other eligible patients might have been missed because of being too sick, busy to attend appointments, or they asked other persons to pick up their medications. Furthermore, self-reported adherence is prone to recall and social desirability bias that might overestimate adherence[24], even though it has been reported to be able to predict virologic failure better than or equally well as objective measures.[25] In addition, a self-reported measure could not identify a pattern of treatment interruption or the distribution of missed doses that determines whether the therapeutic effect of ART is maintained. Thus, an electronic monitoring device may be used in future studies to capture real-time dose intake when the objective is to identify patients at risk of viral rebound.[26,27] Objective measurement to monitor drug levels in the body may be performed using plasma or less-invasive samples (e.g., saliva, urine, dried blood spots) to obtain more granular adherence data.[28] Furthermore, a cross-sectional design could not capture the dynamic process of adherence that may change over time. Longitudinal studies with the use of a combination of adherence measures may be beneficial in this setting to understand and explore more factors impacting treatment adherence in the longer term, including psychological and health system-related factors.

CONCLUSIONS

A high proportion of patients with HIV were highly adherent to ART, had suppressed viral load, and improved CD4. Having secondary education or lower increased the risk of being less adherent to ART. Taking NNRTIs-based ART regimen was associated with good treatment outcomes. Being diagnosed with HIV stage 4 and less adherent to ART were associated with poor virological response, while advanced HIV disease at diagnosis increased the risk of poor immune recovery. Strategies to improve treatment adherence, virological, and immunological outcomes are therefore needed.

ABBREVIATIONS

ART: antiretroviral therapy
CI: confidence interval
HIV: human immunodeficiency virus
INSTI: integrase strand transfer inhibitor
IQR: interquartile range
NNRTI: non-nucleoside reverse transcriptase inhibitor
NRTI: nucleoside/nucleotide reverse transcriptase inhibitor
OR: odds ratio
PI: protease inhibitor
SERAD: self-reported adherence
WHO: World Health Organization

AUTHORS' CONTRIBUTIONS

Zamrotul Izzah: Conceptualization, Investigation, Methodology, Formal analysis, Writing – original draft; Budi Suprapti: Conceptualization, Formal analysis, Supervision, Writing – review and editing; Tri P. Asmarawati: Data curation, Investigation, Writing – review and editing; Christoffer Åberg: Conceptualization, Supervision, Writing – review and editing; Daan J. Touw: Conceptualization, Supervision, Writing – review and editing.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary Text

Bahasa Indonesia version of the Self-Reported Adherence (SERAD) questionnaire

SERAD 1.1

Kode Subyek: **Penilaian Data** Petugas: Tanggal:

A	B	C	D	E	F	G	H	I	J	K	L	M	N
						MINGGU LALU				BULAN LALU			
Jam	Nama Obat	Jumlah tablet		Berapa kali dosis obat tidak digunakan	Jumlah tablet yang tidak digunakan per dosis	Alasan tidak menggunakan obat dan frekuensi (cth: A3; B1)	Berapa kali cara penggunaan obat tidak sesuai jadwal/aturan	Alasan tidak sesuai jadwal/ aturan dan frekuensi (cth: A3; F1)	Berapa kali dosis obat tidak digunakan	Jumlah tablet yang tidak digunakan per dosis	Alasan tidak menggunakan obat dan frekuensi (cth: A3; B1)	Berapa kali cara penggunaan obat tidak sesuai jadwal/aturan	Alasan tidak sesuai jadwal/ aturan dan frekuensi (cth: A3; F1)
			☐										
			☐										
			☐										
	SARAPAN												
			☐										
			☐										
			☐										
			☐										
	MAKAN SIANG												
			☐										
			☐										
			☐										
			☐										
	MAKAN MALAM												
			☐										
			☐										
			☐										
			☐										
	WAKTU:	TOTAL C	☐ TOTAL D	TOTAL E	TOTAL F	A_G I_G B_G J_G C_G K_G D_G L_G E_G M_G F_G N_G G_G O_G H_G	TOTAL H	A_I I_I B_I J_I C_I K_I D_I L_I E_I M_I F_I N_I G_I O_I H_I	TOTAL J	TOTAL K	A_L I_L B_L J_L C_L K_L D_L L_L E_L M_L F_L N_L G_L O_L H_L	TOTAL M	A_N I_N B_N J_N C_N K_N D_N L_N E_N M_N F_N N_N G_N O_N H_N
	menit												

A) Tidak menggunakan obat sesuai waktu terjadwal
B) Lupa
C) Menghindari efek samping
D) Tertidur
E) Berada pada kondisi lain yang tidak sesuai dengan aturan penggunaan obat
F) Menghindari perhatian orang lain saat penggunaan obat
G) Perubahan rutinitas harian (liburan atau akhir pekan)
H) Sakit
I) Terlalu banyak jumlah tablet yang digunakan
J) Merasa depresi atau tidak termotivasi
K) Kehabisan stok obat
L) Tidak mau menggunakan obat
M) Petunjuk dokter
N) Salah paham dengan resep dokter
O) Lainnya

Lebih dari sebulan lalu, berapa kali anda ingat tidak menggunakan obat anda?
☐ Tidak ada
☐ 1 atau 2 kali
☐ 3 atau 5 kali
☐ 6 atau 10 kali
☐ 11 kali atau lebih
Alasan tidak menggunakan obat:

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PERTANYAAN PENANYA
RIWAYAT MINGGU LALU

KOLOM A/B/C: "Biasanya, bagaimana jadwal penggunaan obat anda? Jam berapa umumnya anda menggunakan obat?

KOLOM E: "Seminggu terakhir, sejak Selasa/Rabu/…lalu, apa anda ingat saat tidak menggunakan obat anda dengan alasan apapun?

KOLOM G: Apa anda ingat kenapa anda tidak bisa menggunakan obat anda? *(tulis kode alasan dan berapa kali)*

KOLOM H: "Sebagaimana anda ketahui, dengan obat ini penting untuk mengikuti jadwal penggunaan dan cara pakai (dengan atau tanpa makanan). Seminggu terakhir, sejak Selasa/Rabu/Kamis/…lalu, apa anda ingat untuk menggunakan obat anda dua jam sebelum atau setelah waktu makan anda biasanya? Apakah juga saat akhir pekan atau liburan?

KOLOM I: Apa anda ingat kenapa anda tidak bisa mengikuti jadwal penggunaan obat?

Setelah evaluasi ini, informasi akan dikumpulkan berdasarkan data bulan lalu. Periode ini termasuk juga minggu lalu, jadi bila pasien merujuk pada lebih banyak dosis obat terlewat, hal ini harus ditambahkan pada data minggu terakhir

PERTANYAAN PENANYA
RIWAYAT BULAN LALU

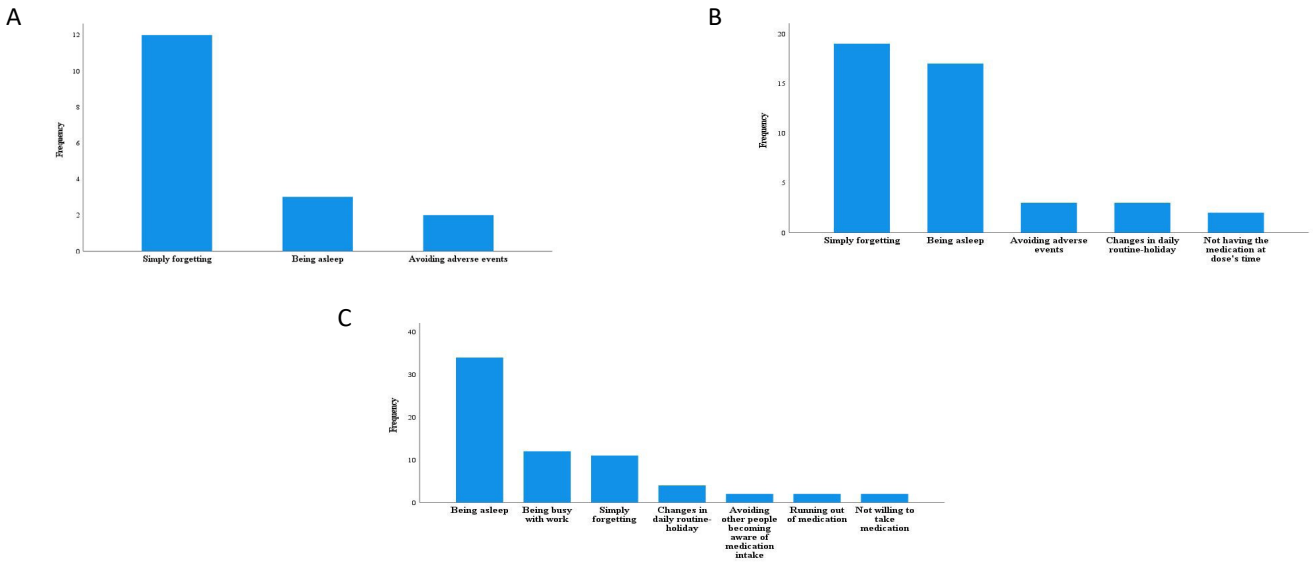
KOLOM J: "Sebulan terakhir, apa anda ingat saat tidak menggunakan obat anda dengan alasan apapun?

KOLOM L: Apa anda ingat kenapa anda tidak bisa menggunakan obat anda? *(tulis kode alasan dan berapa kali)*

KOLOM M: Sebulan terakhir, apa anda ingat untuk menggunakan obat anda dua jam sebelum atau setelah waktu makan anda biasanya? Apakah juga saat akhir pekan atau liburan?

KOLOM N: Apa anda ingat kenapa anda tidak bisa mengikuti jadwal penggunaan obat?

Adapted from the original copyrighted instrument (in English) developed by Muñoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Assessing self-reported adherence to HIV therapy by questionnaire: the SERAD (Self-Reported Adherence) study. AIDS Res Hum Retroviruses. 2007;23(10):1166-1175.



Supplementary Figure S1 Reasons reported for not taking antiretroviral drugs in the last week, last month, and last three months among outpatients with HIV. Forgetfulness was the most common self-reported reason for doses missed during the last week (**A**) and the last month (**B**), while being asleep was the most common reason for missed doses during the last three months (**C**).

HIV=human immunodeficiency virus

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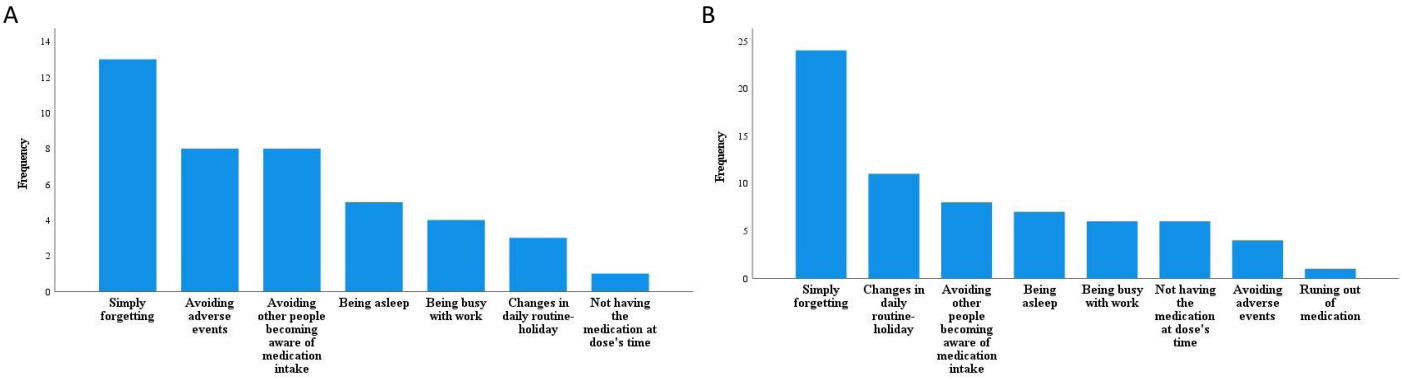

Supplementary Figure S2 Reasons reported for intake conditions not being observed in the last week and last month among outpatients with HIV. Forgetfulness was the most reported reasons for not respecting intake conditions during the last week (**A**) and the last month (**B**).

HIV=human immunodeficiency virus

Supplementary Table S1 Bivariate analysis for variable associated with low adherence to antiretroviral therapy in the past month among outpatients with HIV

Variable	Adherence to ART, n (%)		OR (95% CI)	*p*-value
	Less adherent[a] (N=11)	Highly adherent (N=84)		
Age (years) Median (IQR)	30.0 (28.0–35.0)	35.0 (29.3–42.8)	0.93 (0.86–1.01)	0.10
Sex				
Female	4 (36.4)	24 (28.6)	1.00	
Male	7 (63.6)	60 (71.4)	0.70 (0.19–2.61)	0.60
Education level				
College/university	2 (18.2)	42 (50.0)	1.00	
High school or lower	9 (81.8)	42 (50.0)	4.50 (0.92–22.08)	0.06
WHO HIV clinical stage at diagnosis				
1	4 (36.4)	26 (31.0)	1.00	
2	1 (9.1)	24 (28.6)	0.27 (0.03–2.60)	0.26
3	4 (36.4)	21 (25.0)	1.24 (0.28–5.55)	0.78
4	2 (18.2)	13 (15.5)	1.00 (0.16–6.19)	1.00
Time since HIV diagnosis (months) Median (IQR)	21.0 (9.0–43.0)	35.0 (16.3–55.3)	0.98 (0.95–1.01)	0.15
Duration of ART (months) Median (IQR)	20.0 (9.0–43.0)	30.5 (15.0–49.0)	0.98 (0.95–1.02)	0.30
Type of ART regimen				
NNRTIs-based	11 (100.0)	67 (79.8)	1.00	
INSTIs-based	0	10 (11.9)	0.00	1.00
PIs-based	0	2 (2.4)	0.00	1.00
Triple NRTIs	0	5 (6.0)	0.00	1.00
Number of tablets taken daily Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–4.0)	0.62 (0.35–1.13)	0.12

Note: [a] Less adherent was defined by having an adherence of 95% and lower with regard to the doses missed in the past month.

ART=antiretroviral therapy; CI=confidence interval; HIV=human immunodeficiency virus; INSTI=integrase strand transfer inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside/nucleotide reverse transcriptase inhibitor; OR=odds ratio; PI=protease inhibitor; WHO=World Health Organization

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Supplementary Table S2 Bivariate analysis for variable associated with non-suppressed viral load among patients with HIV at an Indonesian clinic

Variable	Viral load, n (%)		OR (95% CI)	*p*-value
	Non-suppression[a] (N=16)	Suppression (N=79)		
Age (years) Median (IQR)	30.5 (29.0–47.0)	35.0 (29.0–41.0)	1.00 (0.96–1.05)	0.92
Sex				
Female	3 (18.8)	25 (31.6)	1.00	
Male	13 (81.3)	54 (68.4)	2.01 (0.52–7.68)	0.31
Education level				
College/university	6 (37.5)	38 (48.1)	1.00	
High school or lower	10 (62.5)	41 (51.9)	1.55 (0.51–4.66)	0.44
WHO HIV clinical stage at diagnosis				
1	1 (6.3)	29 (36.7)	1.00	
2	2 (12.5)	23 (29.1)	2.52 (0.22–29.58)	0.46
3	6 (37.5)	19 (24.1)	9.16 (1.02–82.21)	0.048
4	7 (43.8)	8 (10.1)	25.38 (2.71–237.57)	0.005
Time since HIV diagnosis (months) Median (IQR)	45.0 (10.5–56.0)	30.0 (16.0–52.0)	1.00 (0.98–1.02)	0.92
Duration of ART (months) Median (IQR)	41.5 (10.3–56.0)	28.0(15.0–48.0)	1.01 (0.99–1.03)	0.30
Type of ART regimen				
INSTIs-based	6 (37.5)	4 (5.1)	1.00	
NNRTIs-based	7 (43.8)	71 (89.9)	0.07 (0.02–0.29)	<0.001
PIs-based	2 (12.5)	0	N/A	1.00
Triple NRTIs	1 (6.3)	4 (5.1)	0.17 (0.01–2.09)	0.16
Number of tablet(s) taken daily Median (IQR)	1.0 (1.0–4.3)	1.0 (1.0–4.0)	1.01 (0.76–1.34)	0.95
Last month adherence				
Highly adherent	11 (68.8)	73 (92.4)	1.00	
Less adherent	5 (31.3)	6 (7.6)	5.53 (1.44–21.24)	0.01
Last 3-month adherence				
Highly adherent	15 (93.8)	76 (96.2)	1.00	
Less adherent	1 (6.3)	3 (3.8)	1.69 (0.16–17.36)	0.66

Note: [a] Viral load non-suppression was defined by having a viral load of 1,000 copies/ml and higher.

ART=antiretroviral therapy; CI=confidence interval; HIV=human immunodeficiency virus; INSTI=integrase strand transfer inhibitor; N/A=not available; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside/nucleotide reverse transcriptase inhibitor; OR=odds ratio; PI=protease inhibitor; WHO=World Health Organization

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Supplementary Table S3 Bivariate analysis for variable associated with low CD4 cell count among patients with HIV at an Indonesian clinic

Variable	CD4 cell count, n (%)		OR (95% CI)	*p*-value
	Low[a] (N=30)	High (N=65)		
Age (years) Median (IQR)	37.0 (29.0–45.3)	35.0 (29.0–41.0)	1.01 (0.97–1.05)	0.63
Sex				
Female	4 (13.3)	24 (36.9)	1.00	
Male	26 (86.7)	41 (63.1)	3.81 (1.18–12.22)	0.03
Education level				
College/university	12 (40.0)	32 (49.2)	1.00	
High school or lower	18 (60.0)	33 (50.8)	1.46 (0.61–3.50)	0.40
WHO HIV clinical stage at diagnosis				
1	2 (6.7)	28 (43.1)	1.00	
2	7 (23.3)	18 (27.7)	5.44 (1.02–29.19)	0.048
3	11 (36.7)	14 (21.5)	11.00 (2.14–56.57)	0.004
4	10 (33.3)	5 (7.7)	28.00 (4.67–168.00)	<0.001
Time since HIV diagnosis (months) Median (IQR)	32.0 (13.8–53.0)	33.0 (21.5–53.0)	0.99 (0.98–1.01)	0.46
Duration of ART (months) Median (IQR)	26.5 (12.8–49.5)	29.0 (16.0–49.0)	1.00 (0.98–1.02)	0.94
Type of ART regimen				
INSTIs-based	6 (20.0)	4 (6.2)	1.00	
NNRTIs-based	19 (63.3)	59 (90.8)	0.22 (0.06–0.84)	0.03
PIs-based	2 (6.7)	0	N/A	1.00
Triple NRTIs	3 (10.0)	2 (3.1)	1.00 (0.11–8.95)	1.00
Number of tablet(s) taken daily Median (IQR)	1.5 (1.0–4.0)	1.0 (1.0–4.0)	1.01 (0.80–1.26)	0.95
Last month adherence				
Highly adherent	25 (83.3)	59 (90.8)	1.00	
Less adherent	5 (16.7)	6 (9.2)	1.97 (0.55–7.04)	0.30
Last 3-month adherence				
Highly adherent	29 (96.7)	62 (95.4)	1.00	
Less adherent	1 (3.3)	3 (4.6)	0.71 (0.07–7.15)	0.77

Note: [a] Low CD4 cell count was defined by having CD4 less than 200 cells/mm^3.

ART=antiretroviral therapy; CI=confidence interval; HIV=human immunodeficiency virus; INSTI=integrase strand transfer inhibitor; IQR=interquartile range; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside/nucleotide reverse transcriptase inhibitor; OR=odds ratio; PI=protease inhibitor; WHO=World Health Organization

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