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Factors associated with anti-retroviral therapy adherence among patients living with HIV during the COVID-19 pandemic: A cross-sectional study

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Background: The coronavirus disease (COVID-19) pandemic causes fear and anxiety symptoms on some vulnerable populations such as patients living with human immunodeficiency virus (HIV) (PLWH). Physical distancing (during consultation in the clinic) and isolation restrictions will likely have a negative impact on/disruption to all care continuum services of HIV diseases although healthcare services and access to anti-retroviral therapy (ART) have continued to operate.

Objective: To investigate the factors associated with ART adherence among PLWH during the COVID-19 pandemic.

Methodology: A cross-sectional study was conducted on 324 PLWH who had been on ART for at least 6 months between June 2020 and January 2021. A semi-structured questionnaire was used to interview participants to collect data on sociodemographic characteristics and other factors.

Results: Of 324 PLWH taking ART, 264 (81.48%) had high adherence ($\geq 95\%$) and 60 (18.52%) had low adherence ($< 95\%$). Factors independently associated with high ART adherence were employment status (adjusted odds ratio (AOR): 0.030, 95% confidence interval (CI): 0.010–0.088; $p < 0.001$), type of antiretroviral (ARV) (AOR: 3.101, 95% CI: 1.137–8.456; $p = 0.027$), family support (AOR: 0.157, 95% CI: 0.052–0.475; $p = 0.001$), the perception that the COVID-19 pandemic negatively impacts the ability to attend clinics (AOR: 7.339, 95% CI: 1.46–36.79; $p = 0.015$), and the perception that the COVID-19 pandemic negatively impacts the ability to take ART (AOR: 10.611, 95% CI: 2.98–37.72; $p < 0.001$).

Conclusions: During the COVID-19 pandemic, factors associated with high ART adherence among PLWH attending the Hospital of Wangaya in Denpasar, Bali, Indonesia were employment status, ART type [non-fixed dose combination (FDC)], family support, and the perception that the COVID-19 pandemic negatively impacts the ability to attend clinics and to take ART.

KEYWORDS

adult PLWH, COVID-19 pandemic, anxiety disorder, ART adherence, anti-retroviral therapy

Introduction

Anti-retroviral therapy (ART) has been shown to be effective in suppressing viral replication, altering the natural course of the disease, and lowering morbidity and mortality (1–4). Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) continue to be major global public health issues (3, 5–7). It is now understood that HIV infection is a chronic inflammation that is potentially treatable. As a result, new conditions associated with the chronicity of the disease, such as ART adherence, have emerged (8). ART adherence is critical to long-term treatment success, therefore therapy has become a major source of concern. High ART adherence can reduce morbidity and mortality and improve the quality of life of patients living with HIV (PLWH).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause a wide variety of symptoms, ranging from asymptomatic carriage to moderate flu-like symptoms to severe pneumonia and respiratory failure requiring admission to an intensive care unit (ICU) (9). Since the beginning of the pandemic, several publications have been published, both on the link between HIV and an increased risk of acquiring symptomatic SARS-CoV-2 infection and on the poor prognosis of the new 2019 coronavirus disease (COVID-19) in PLWH (10). The COVID-19 pandemic has now become a health and psychosocio-economic threat, and potentially cause fear, anxiety, and distress among PLWH because of how COVID-19 may impact their lives (9). In Indonesia, a total of 2,135,998 COVID-19 cases had been confirmed as of 28 June 2021 (10). Following the Eid al-Fitr celebrations in May, Indonesia experienced a spike in COVID-19 cases nationwide, following a downward trend in cases and deaths in March. A significant increase in lodging occupancy rates in high-risk provinces since the beginning of June is a source of great concern. As of 28 June 2021, 19,616,389 exams had been conducted. By the end of June, daily testing had risen from roughly 50,000 tests/day in March to close to 74,000 tests/day. As of June, the national test positivity rate was 23.2 per 100,000 (10).

Access to ART is a critical public health priority during the COVID-19 pandemic. Improving adherence necessitates

collaboration with patients to identify and address individual barriers to COVID-19 and adherence (11–14).

This study investigated factors associated with ART adherence among PLWH during the COVID-19 pandemic.

Methodology

Study population and design

A cross-sectional study enrolled PLWH who visited Wangaya Hospital, in Denpasar, Bali between June 2020 and January 2021 and were included in the study on the basis of (1) receiving ART for at least 6 months; (2) being willing to be interviewed; and (3) giving written or verbal informed consent. There were 324 participants who took part in this study. All PLWH should receive a psychosocial approach who gave written informed consent during the visit every 30 days on a routine basis. Participants were questioned about their sociodemographic characteristics and the length of time they had been taking ART. Age, gender, education, the status of employment/occupation, address (travel burdens), antiretroviral (ARV) type, support, and the perception that the COVID-19 pandemic has a negative impact on patient's ability to visit clinics, and the perception that the COVID-19 pandemic has a negative impact on the ability to take ART were the factors associated with ART adherence among PLWH. The GAD-7 questionnaire was used to assess anxiety disorders (ADs), with the sensitivity and specificity of this tool using the optimal cutoff point being 89 and 82%, respectively. The severity of AD was classified into two groups: non-severe AD, mild to moderate anxiety (GAD-7 score ≤ 10), and severe AD (GAD-7 score > 10) (9).

Adherence measurement

In this study, self-report was used to measure adherence. This method was considered to be simple, practical, inexpensive, flexible, and of short duration. It was also confirmed by pill counts, which consisted of determining the number of pills

remaining in patients' bottles. Patients returned the pill bottles, so that clinicians could physically count the remaining pills. Pill counts were determined retrospectively using a 30-day recall. The adherence index was calculated by the formula (15):

$$\frac{\text{Total number of drugs taken (for 30 days)}}{\text{Total number of drugs prescribed (for 30 days)}} \times 100$$

Patients living with HIV with $\geq 95\%$ adherence were considered to have high adherence, while those with $< 95\%$ were considered to have low adherence (16–19).

Statistical analysis

The data were analyzed with the Statistical Package for Social Sciences (SPSS), statistics for Windows version 26.0. To characterize the study population status, we report numbers and proportion for categorical variables and means with standard deviation (SD) for normally distributed continuous variables and median with interquartile range for non-normally distributed variables. Bivariate analysis was used to calculate crude odds ratios (OR) with 95% confidence intervals (CIs) to investigate the relationship between the independence variables, including sociodemographic and other characteristics and ART adherence. The Chi-squared test or Fisher's exact test was used for categorical variables, *t*-test for normally distributed continuous variables, the Mann–Whitney *U*-test for non-normally distributed continuous variables, and the Kruskal–Wallis test for ordinal variables, and a $p < 0.05$ was considered statistically significant.

Ethical clearance

The approval to conduct this study was granted by local ethical committees. Ethical clearance no 09/RSUDW/Litbang/2020 was obtained. The study was carried out in accordance with the Declaration of Helsinki. Patients who visited Wangaya Hospital, in Denpasar, Bali, Indonesia provide us with data, which we then analyzed. All participants were asked to give informed consent.

Results

In this study, the baseline characteristics among 324 participants are included and are described in detail in Table 1. Overall, 81.48% (264/324) of the participants were reported with high adherence, but 18.52% (60/324) of the participants were reported with low adherence (Table 2).

There is a statistically significant relationship between high adherence with older age (≥ 34 -year old) ($p = 0.03$), employment

TABLE 1 Characteristic data of the participants ($n = 324$).

Variables	N (%) / Mean \pm SD
Age (year)*	
<34	153 (47.2%)
≥ 34	171 (52.8%)
Sex	
Male	197 (60.8%)
Female	127 (39.2%)
Education	
Uneducated	6 (1.9%)
Elementary school	45 (13.9%)
Junior high school	58 (17.9%)
High school	186 (57.4%)
University	29 (9.0%)
Employment status	
Employed	250 (77.2%)
Unemployed	74 (22.8%)
Address	
In Denpasar	242 (74.7%)
Out of Denpasar	82 (25.3%)
Type of ARV	
FDC	166 (51.2%)
Non-FDC	158 (48.8%)
Support	
No support	102 (31.5%)
Family	116 (35.8%)
NGO	106 (32.7%)
Anxiety disorder (AD)	
Severe anxiety disorder (GAD-7: > 10)	124 (38.3%)
Non-severe anxiety disorder (GAD-7: ≤ 10)	200 (61.7%)
Measure assessed at post-lockdown assessment	
Perception that COVID-19 pandemic negatively impacts ability to come to clinic	139 (42.9%)
Perception that COVID-19 pandemic negatively impacts ability to take ART	75 (23.1%)

*, Age in median.

status/employed ($p < 0.01$), ARV type (due to adverse effect) ($p < 0.01$), family support ($p < 0.01$), and non-severe anxiety ($p < 0.01$). The perception that the COVID-19 pandemic negatively impacts the ability to attend clinics and to take ART showed a statistically significant association ($p < 0.01$) (Table 2).

In this study, we discovered a statistically significant relationship between high ART adherence and older age, employment status/employed, ARV type (due to adverse effects), family support, education, non-severe anxiety, and the perception that the COVID-19 pandemic had a negative impact on the ability to visit clinics and to take ART but no association with sex, education, and address.

TABLE 2 Associated factors to adherence levels among PLWH ($n = 324$).

Variables	High adherence $N = 264$ (81.48%)	Low adherence $N = 60$ (18.52%)	p -value
Age (year)*			
<34	118 (44.7%)	35 (58.3%)	$p = 0.03$
≥ 34	146 (55.3%)	25 (41.7%)	
Sex			
Male	165 (62.5%)	32 (53.3%)	$p = 0.12$
Female	99 (37.5%)	28 (46.7%)	
Education			
Uneducated	4 (1.5%)	2 (3.3%)	$p = 0.60$
Elementary school	35 (13.3%)	10 (16.7%)	
Junior high school	45 (17.0%)	13 (21.7%)	
High school	155 (58.7%)	31 (51.7%)	
University	25 (9.5%)	4 (6.7%)	
Employment status			
Employed	234 (88.6%)	16 (26.7%)	$p < 0.01$
Unemployed	30 (11.4%)	44 (73.3%)	
Address			
In Denpasar	195 (73.9%)	47 (78.3%)	$p = 0.29$
Out of Denpasar	69 (26.1%)	13 (21.7%)	
Type of ARV			
FDC	120 (45.5%)	46 (76.7%)	$p < 0.01$
Non-FDC	144 (54.5%)	14 (23.3%)	
Support			
No supported	88 (33.3%)	14 (23.3%)	$p < 0.01$
Family	112 (42.4%)	4 (6.7%)	
NGO	64 (24.2%)	42 (70.0%)	
Anxiety disorder (AD)			
Severe anxiety disorder (GAD-7: >10)	79 (29.9%)	45 (75.0%)	$p < 0.01$
Non-severe anxiety disorder (GAD-7: ≤ 10)	185 (70.1%)	15 (25.0%)	
Measure assessed at post-lockdown assessment			
Perception that COVID-19 pandemic negatively impacts ability to come to clinic	90 (34.1%)	49 (81.7%)	$p < 0.01$
Perception that COVID-19 pandemic negatively impacts ability to take ART	174 (65.9%)	11 (18.3%)	$p < 0.01$

ARV, anti-retroviral; FDC, fixed dose combination; NGO, non-government organization; GAD, generalized anxiety disorders; COVID, coronary virus disease.

*. Age in median.

In the bivariate analysis, there was a statistically significant association between older age (≥ 34 -year old) and high ART adherence ($p = 0.03$). Employment status/employed had a statistically significant association with high ART adherence ($p < 0.01$). We reported that the ARV type (due to the side effects of ARV) had a statistically significant relationship with high ART adherence ($p < 0.01$). Due to the perception that the COVID-19 pandemic had a negative impact on the ability to visit clinics and take ART, this study found a statistically significant association between the COVID-19 pandemic and high ART adherence ($p < 0.01$) (Table 2).

The multivariate analysis was done by logistic regression, and we found a statistically significant association between employment status (adjusted odds ratio (AOR): 0.030, 95% CI: 0.010–0.088; $p < 0.001$), the type of ARV (AOR: 3.101, 95% CI: 1.137–8.456; $p = 0.027$), support (AOR: 0.157, 95% CI: 0.052–0.475; $p = 0.001$), the perception that the COVID-19 pandemic negatively impacts the ability to come to clinics (AOR: 7.339, 95% CI: 1.46–36.79; $p = 0.015$), and the perception that the COVID-19 pandemic negatively impacts the ability to take ART (AOR: 10.611, 95% CI: 2.98–37.72; $p < 0.001$), with adherence levels among PLWH (Table 3).

TABLE 3 Multivariate analysis of adherence levels among PLWH ($n = 324$).

Variables	AOR	95%CI	P-value
Age (years)	2.108	0.703–6.319	0.183
Anxiety disorders	0.732	0.154–3.493	0.696
Employment status	0.030	0.010–0.088	<0.01
Type of ARV	3.101	1.137–8.456	0.027
Support	0.157	0.052–0.475	0.001
Perception that COVID-19 pandemic negatively impacts ability to come to clinic	7.339	1.46–36.79	0.015
Perception that COVID-19 pandemic negatively impacts ability to take ART	10.611	2.98–37.72	<0.01

ARV, antiretroviral; ART, antiretroviral therapy, COVID-19, coronavirus disease 2019.

Discussion

In the management of chronic diseases, including HIV infection, ART adherence is also a major issue (16, 20). According to HIV studies, high ART adherence is required for viral suppression, prevention of ART resistance and disease progression, and decreased risk of transmission (17–20). A variety of factors influence ART adherence, such as drug toxicity and regimen complexity (21, 22).

In this study, 324 participants were involved, of whom 81.48% (264 participants) reported high adherence ($\geq 95\%$ of their pills were taken in the previous 30 days) and 18.52% (60 participants) reported low adherence ($< 95\%$ of their pills were taken in the previous 30 days). This was different from our previous study (prior COVID-19 pandemic); among 202 participants. Of these, 84.16% (170/202) had high ART adherence and 15.84% (32/202) had low ART adherence (23).

In this study, older age (≥ 34 -year old) was not associated with high ART adherence (AOR = 2.108; 95% CI: 0.703–6.319, $p = 0.183$). On the other hand, Tolossa et al. (24) reported that the odds of non-adherence to ART were 3.41 times higher among patients younger than 25 years as compared to their counterpart (OR = 3.41, 95% CI: 1.26–9.21) (24).

Employment status/employed has a statistically significant association with high ART adherence (AOR = 0.030; 95%CI: 0.010–0.088, $p < 0.01$). Prah et al. (20) found that employment status/employed was significantly related to ART adherence ($p < 0.01$) (20). Also Safira et al. (16) reported that employed had a statistically significant association with high ART adherence ($p = 0.03$) (16). Suleiman et al. (17) found that employment was significantly associated with high ART adherence ($p < 0.01$) (17). According to Ibrahim et al. (18), those who were unemployed were more likely to fail to comply with ART ($p =$

0.01) (18). According to Talam et al. (19), high ART adherence was associated with employment ($p = 0.01$) (19).

Furthermore, other factors contribute to the effectiveness of ART, such as participants' ability to follow particular instructions regarding dose intervals as a result of regular ARV use (25–27).

We reported that ARV type (due to the side effects of ARV) had a statistically significant relationship with high ART adherence (AOR = 3.101; 95% CI: 1.137–8.456, $p = 0.027$). Cheng et al. (27) found that ARV type (treatment side effect) was associated with high ART adherence ($p < 0.01$) (27). According to Achappa et al. (28), ART side effects were significantly associated with ART adherence ($p < 0.01$) (28). According to Oliveira et al. (1), adverse drug effects were associated with ART adherence ($p < 0.01$) (1). Shigdel et al. (29) found that the adverse effects of ARV were related to therapy adherence ($p < 0.05$) (29).

The support of family increases the patient's self-esteem, making it easier for the patient to stick to ART and suggest that the patient will be alive for a long time and in good health. In contrast, if a patient lacks support, the patient's situation becomes more difficult because what follows is ill-treated from the family, and the person loses hope, which leads to treatment failure (11). In this study, we found that family support was statistically significantly associated with high ART adherence (AOR = 0.157; 95% CI: 0.052–0.475, $p = 0.001$). Another study conducted by Achappa et al. (28) reported that good family support was statistically significantly associated with high ART adherence ($p < 0.01$). According to a meta-analysis, participants from cohesive families have 1.74 times higher adherence (28). Yathiraj et al. (30) discovered that participants with a strong family support (74%; OR = 3.0, CI = 1.2, 5.2) were more likely to adhere to ART ($p < 0.05$) (30). According to Joseph et al. (31), family support was statistically associated with high ART adherence ($p < 0.01$) (31).

Anxiety is an adaptive emotional and behavioral response to threatening stimuli that is necessary for survival, characterized by chronic and persistent worry. Factors that may be associated with anxiety include health, finances (due to job loss), physical distancing, social isolation, and school closures, as occurred during the COVID-19 pandemic (14, 32, 33).

This study reported no statistically significant association between high ART adherence and non-severe anxiety (AOR = 0.732; 95% CI: 0.154–3.493, $p = 0.696$). The study conducted in India reported that AD was found in 39.5% of 152 participants. Another study found that the lower proportions of AD 13.0% in Wuhan and 10.8% in Singapore (34–36). There was a significantly higher frequency of participants with anxiety vs. without anxiety in Bangladeshi during the COVID-19 pandemic (96.1 vs. 69.8%, $p < 0.01$) (33).

Due to the perception that the COVID-19 pandemic has negatively affected the ability to visit clinics and the ability to take ART, this study found a statistically significant association

with high ART adherence (AOR = 7.339; 95%CI: 1.46–36.79, $p = 0.015$; AOR = 10.611; 95% CI: 2.98–37.72, $p < 0.01$, respectively). It is clear from this study that COVID-19 has adversely affected the capacity of many PLWH to attend the clinic and their ability to take ART. Client travel to HIV clinics during COVID-19 has become difficult due to the lack of transportation, staff checks during the lockdown, and the lack of funds to pay for transportation, and PLWH were afraid of being infected when visiting the clinic. Dorward et al. (37) reported that ART initiation reduced from a weekly median of 571 prior to lockdown (interquartile ranges (IQR) 498–678) to 375/week after lockdown (331–399), in the 1st week of lockdown, the Poisson regression model estimated to have decreased by 46.2% (30 March 2020 to 5 April 2020; IRR 0.538, 0.459–0.630) (37). Dear et al. (38) reported that during the early COVID-19 period, PLWH were less likely to be adherent to HIV clinic visits (adjusted OR: 0.64; 95% CI: 0.45–0.91); however, this association was not significant in the late COVID-19 period (AOR: 0.82; 95%CI: 0.57–1.19) (38).

In this study, we discovered no relationship between high ART adherence and gender, education, or address (travel burdens). Other studies reported no association between ART adherence and sex, education, or income (38). According to Byabene et al. (39), high ART adherence was not associated with time to the clinic (travel burdens) ($p = 0.07$) (39).

Conclusion

Generally, participants have high ART adherence. There is a higher proportion/percentage of participants with high ART adherence in our previous study (before the COVID-19 pandemic) than during the COVID-19 pandemic. High ART adherence is statistically significantly associated with employment, the type of ARV being used, family support, and the perception that the COVID-19 pandemic negatively impacts the ability to attend clinics and to take ART.

Limitations

This study had some drawbacks, including a small sample size. Between June 2020 and January 2021, this study was conducted in a single center at Wangaya Hospital in Denpasar, Bali-Indonesia. The use of a cross-sectional design limited the degree to which causal inferences and generalizations could be made from the research findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Wangaya Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KS contributed to the concept of the research idea, study design, data analysis, and paper drafting. HS contributed to the design study and the revision of this paper. AI and LW contributed to the data collection, paper drafting, and the revision of this paper. WP and NY contributed to the data collection and the revision of this paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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