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Effects of depression on medication adherence in HIV/AIDS patients: Korea HIV/AIDS cohort study

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ABSTRACT

Background: The number of people with HIV/AIDS has consistently increased in Korea since the first case of HIV/AIDS infection was reported in 1985. The depressive symptoms of patients with HIV/AIDS may lead to medication non-adherence. This study sought to investigate the cross-sectional and longitudinal association between depression and antiretroviral treatment adherence in the Korean HIV/AIDS population.

Methods: We included participants of the Korea HIV/AIDS cohort study between 2009 and 2017. All information was collected at the enrollment and every annual visit, including sociodemographic characteristics, health-related behaviors, HIV/AIDS infection-related factors, depression score, and frequency of skipped medication. We performed a cross-sectional analysis of 601 participants registered between 2009 and 2017. Longitudinal data were evaluated by panel regression analysis in 515 patients who registered from 2009 to 2013.

Results: In cross-sectional analysis, the HIV/AIDS patients with depressive symptoms were more likely to be non-adherent (adjusted OR = 0.52, 95 % CI 0.34, 0.79, p = 0.002). Medication adherence was significantly associated with a health-related lifestyle; the adjusted odds ratio of the non-smoking and non-drinking group was 1.75 (95 % CI 1.05, 2.90, p = 0.031). The longitudinal panel regression model revealed a significant negative impact of depression on medication adherence (adjusted OR = 0.50, 95 % CI 0.30, 0.84, p = 0.009). Non-smoking and non-drinking participants were 2.31 times more likely to adhere to antiretroviral treatment (95 % CI 1.29, 4.15, p = 0.005).

Conclusions: Our finding of depression and lifestyle modifications being significant contributors underscore the importance of proactive interventions to optimize the treatment outcomes of PLWH.

Introduction

The number of people with HIV/AIDS has consistently increased in Korea since the first case of HIV/AIDS infection was reported in 1985. The spread of HIV infection has been accelerating since 2013, adding approximately 1000 new patients with HIV/AIDS infections per year [1]. As of 2020, the cumulative number of HIV infections in Korea has reached approximately 15,000 persons.[1].

A "treatment as prevention" strategy has been adopted to tackle HIV/AIDS. This pursues antiretroviral treatment and prevention simultaneously to prevent opportunistic infection and secondary transmission by controlling HIV-RNA replication. This can be achieved by improving patient adherence to antiretroviral treatment medication [2–4]. The Joint United Nations Program on HIV/AIDS (UNAIDS) updated its targets to 95–95–95 by 2030: 95 % of individuals living with HIV will recognize their HIV status, 95 % of people with diagnosed HIV infection will be prescribed ART, and 95 % of those taking ART will have achieved viral suppression.

Abbreviations: PLWH, people living with HIV/AIDS; KoCosHIV, Korea HIV/AIDS cohort study; BDI, Beck Depression Inventory; HAART, highly active antiretroviral treatment

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Therefore, it is vital to assess the factors associated with medication adherence among those living with HIV/AIDS [5].

It has been demonstrated through clinical studies that people living with HIV/AIDS (PLWH) who adhere ART medication can effectively maintain a health status comparable to that of the general population [6,7]. Additionally, suppressed viral load has been proven to prevent HIV transmission [8], leading to a new paradigm shift known as "undetectable equals untransmittable". However, information about HIV/AIDS in the general population in Korea tends to be insufficient compared to other countries [9,10]. According to the "Korea HIV Stigma Index Survey" conducted in 2017, 64.4 % of 104 infected individuals in South Korea reported feeling guilty, whereas in Germany, only 22.8 % of infected individuals reported similar feelings [10].

PLWH have to face frustration and desperation as soon as they were diagnosed as HIV/AIDS. Fading relationships with families, friends, and colleagues can cause a loss of emotional stability, depression, and anxiety among PLWH [11,12]. The reported evidence for this relationship implies that depressive symptoms, such as a feeling of worthlessness, and recurrent thoughts of suicide, would affect the loss of willingness to treat. Depressive symptoms lower patient motivation for treatment; therefore, it has a strong association with non-adherence to medication. This can lead to progression of disease and high mortality [3,13,14]. A prior study has suggested that the estimated depression rate is 21 %; depressive patients are more likely to be anxious and they frequently forget out-patient clinical appointments when compared with non-depressive patients in Korea [15].

To the best of the authors' knowledge, no research has investigated the relationship between depression and antiretroviral treatment adherence using longitudinal data. This study was conducted to compare the cross-sectional and longitudinal association between depression and antiretroviral treatment adherence in Korea.

Material and methods

Data sources

We analyzed data from the ongoing Korea HIV/AIDS cohort study (KoCosHIV). This is a prospective observational study of PLWH enrolled in 21 contributing general hospitals. The KoCosHIV was organized by the departments of AIDS and virus diseases of the Korea Disease Control and Prevention Agency in December 2006. Sociodemographic information, medical and epidemiological data, including virological status, are obtained using a standardized survey questionnaire at every 6 months by trained clinical researchers [16].

Study populations

We extracted eligible subjects from KoCosHIV between 2006 and 2017 as follows: ≥ 18 years of age with a depression scale score at KoCosHIV enrollment (N = 839). Of these, samples with no baseline sociodemographic data were excluded (n = 62). After excluding those without adherence scale data at the 6-months follow-up visit (n = 176), a cross-sectional analysis was conducted for the remaining 601 patients.

Longitudinal panel data analysis was performed based on 4-years of follow-up between 2009 and 2013 for 515 patients. Each patient was followed up annually after the enrollment in the KoCosHIV. Since the panel was unbalanced, 2196 observations were included for the four years (Fig. 1, Appendix 1).

Variables

Self-reported medication adherence

Medication adherence was measured by assessing the frequency of skipping antiretroviral treatment at the 6-month follow-up visit after cohort enrollment and subsequent annual follow-up visits. It was rated on a 6-point Likert scale, where higher scores indicate better adherence (1 = skipped daily; 2 = skipped more than twice a week; 3 = skipped once a week; 4 = skipped once in two weeks; 5 = skipped once a month; and 6 = never skipped). We generated a dummy indicator from the original variable for medication adherence as adherent = fully adhered versus not-fully adhered = taking medication with ≥ 1 instance of skipping.

Depressive symptom

Depressive symptoms were assessed using the Beck Depression Inventory (BDI) and the EuroQol five-dimensional (EQ-5D) scale. The BDI is a 21 item self-reported questionnaire including cognitive, emotional, motive, and physiological areas of depression. Each item is scored from 0 to 3 to indicate the degree of severity. The total score can range from 0 to 63. The BDI conducted on the Korean population demonstrated a Cronbach's alpha coefficient of 0.85 on average (0.86 for males and 0.84 for females), indicating a reliable assessment [17]. Depression is defined as having a score ≥ 21 [18,19]. The BDI was measured at KoCosHIV enrollment and annual visits until 2014. The EQ-5D has been replaced for follow-up visits since 2015. The EQ-5D is a generic questionnaire measuring five domains of current health-related quality of life, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A global index ranging from 0 to 3 points indicates a higher health-related quality of life [20]. The anxiety/depression dimension has three levels; 1 = not anxious or depressed; 2 = moderately anxious or depressed; and 3 = extremely anxious or depressed. Scores of 2 or 3 on the anxiety/depression domain were classified as depression in the current study [21].

Covariates

The KoCosHIV collects information on sociodemographic factors, health-related behaviors, and HIV/AIDS infection-related factors at enrollment. Demographic factors include gender, age, and marital status. Exposure of HIV infection was categorized as sexual contact (homosexual, heterosexual, or bisexual). Health-related factors included information on smoking and drinking. These were divided into patients who smoke and drink currently, those who smoke only or drink only, and those who do not smoke nor drink. Comorbidities were categorized according to number (0, 1, or ≥2) of diagnoses: diabetes mellitus, hypertension, dyslipidemia, lipohypertrophy, cardiovascular diseases including acute myocardial infarction, cerebrovascular diseases, ischemia and other heart diseases, tuberculosis, cancer, and other chronic infectious diseases (hepatitis B or C). Duration of prior antiretroviral treatment administration was categorized into < 1 or ≥ 1 year at the cohort enrollment [22]. Patients were also divided into groups according to their antiretroviral treatment regimen: nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase standard transfer inhibitors (INSTIs), and INSTIs and PIs as NRTI sparing [23].

Statistical analysis

The Student's t-test and χ^2 test were used to analyze statistical differences in baseline characteristics. A logistic regression model was conducted to assess the cross-sectional association between depression and medication adherence.

The factors that influence medication adherence were analyzed using a random effects panel regression model. The objective of this

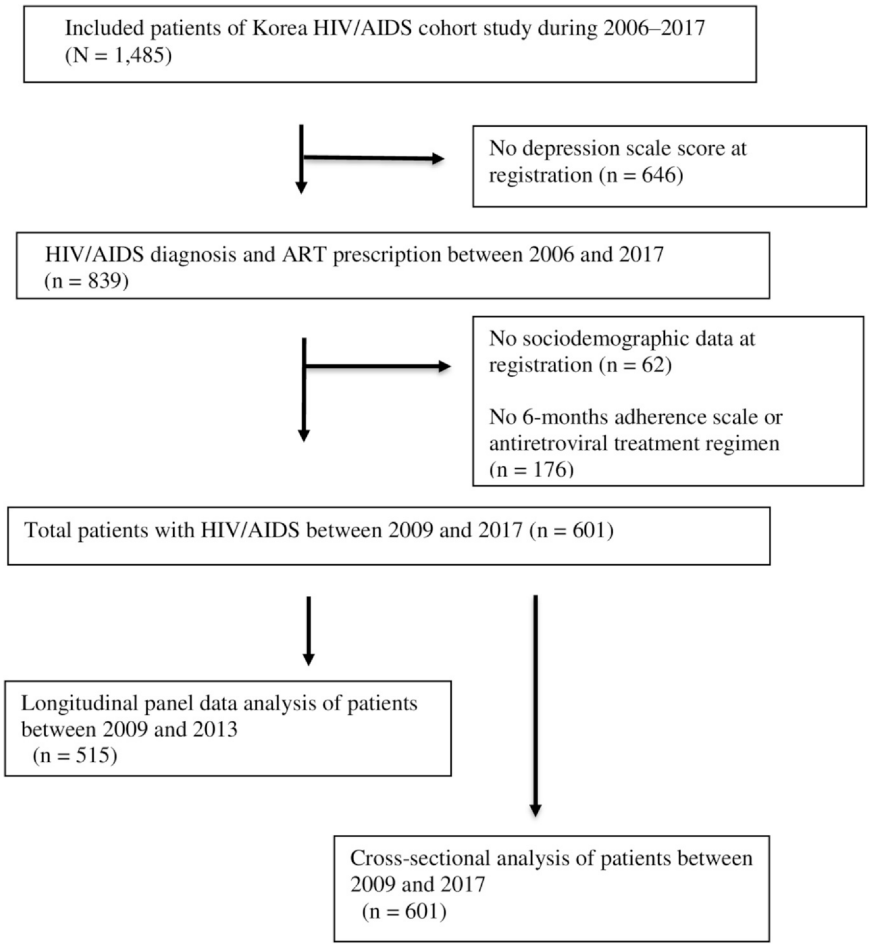

Fig. 1. Flow chart of study sample selection.

panel data analysis was to estimate depression and medication adherence over time using longitudinal cohort data. Medication adherence and depressive symptoms were classified using dichotomous criteria for each individual and time points; therefore, a binomial distribution was expected and the estimation method was specified using the logistic link function. All statistical analyses were performed using STATA 15 (Stata Corp, College Station, TX, USA).

Results

Cross-sectional analysis between depression and medication adherence

The baseline characteristics of the 601 patients for cross-sectional analysis are presented in Table 1. The proportion of fully adhering patients that did not skip ART was 68 % (n = 406). Patients who forgot to take medication more than once accounted for 32 % of the study group (n = 195). Most patients (approximately 95 %) were male. The complete-adherence group had a higher proportion of patients ≥ 60 years of age (p = 0.035). Non-adherence group showed higher proportions of those who smoke and drink (p = 0.003). The average depression score was 13.5 ± 11.1 and 15.0 ± 10.2 in the adherence and non-adherence group, respectively. The prevalence of depressive symptoms was higher in the non-adherence group (29.7 %) than in the adherence group (19.9 %).

In total, 601 patients were included in the cross-sectional analysis (Table 2). PLWH with depressive symptoms were more likely to be non-adherent, while those with a 2NRTI backbone and INSTI in the antiretroviral treatment group and good healthy lifestyle were more adherent. The odds ratio of depressive symptoms was 0.52, which represented a statistically significant predictor of medication non-adherence (95 % CI 0.34, 0.79, p = 0.002). Specifically, medication adherence was related to health-related behaviors. Patients who did not smoke nor consume alcohol were 1.75 × more likely to become adherent than those who did (95 % CI 1.05, 2.90, p = 0.031). Significantly, higher ART adherence was observed in patients taking a 2NRTI backbone plus INSTI in the antiretroviral treatment group after adjusting for other covariates (a.OR = 1.97, 95 % CI 1.20, 3.25, p = 0.008). Furthermore, older patients (≥60 s years) had higher medication adherence than those who were < 40 s of age.

Longitudinal panel data analysis between depression and medication adherence

Summary statistics for 2196 observations from the 515 patients in the panel data are presented in Appendix 2. Each patient was observed 2.8 times on average, and 322 patients completing all visits from wave 1 to wave 4. Regarding dropouts, 96 % of all registered patients completed the wave 1 visit, 80 % of patients attended at the 2-year visit, and 74 % of patients completed the wave 4 follow-up visit. In total, 482 out of 515 individuals (93.6 %) were male. The proportions of self-reported 'never skipped' ART adherence increased persistently over the four years, with 62.1 % (285/459) at baseline, 64.1 % (252/393) at wave 1, 69.8 % (250/358) at wave 2 %, and 70.7 % (219/310) at wave 4. In the ART regimen group, boosted PI and NNRTI accounted for 54.6 % (219/401) and 29.9 % (120/401) of participants at baseline, respectively. The proportion of individuals

Table 1
Baseline characteristics.

Variable	Adherence group (n = 406)	Non-adherence group (n = 195)	p-value
Depressive symptoms	13.5 ± 11.1	15.0 ± 10.2	0.096
Normal	325 (80.1)	137 (70.3)	0.008
Depression	81 (19.9)	58 (29.7)	
Gender			
Male	379 (93.4)	185 (94.9)	0.467
Female	27 (6.6)	10 (5.1)	
Age	42.0 ± 12.7	39.6 ± 11.2	0.023
< 40	183 (45.1)	94 (48.2)	0.035
40–59	181 (44.6)	93 (47.7)	
≥ 60 years	42 (10.3)	8 (4.1)	
Exposure category for HIV infection			
Homosexual	139 (34.2)	73 (37.4)	0.105
Heterosexual	179 (44.1)	69 (35.4)	
Bisexual	88 (21.7)	53 (27.2)	
Marital status			
Unmarried	238 (58.6)	127 (65.1)	0.207
Married	112 (27.6)	41 (21.0)	
Divorced etc.	56 (13.8)	27 (13.9)	
Health-related factor			
Smoke and drink	108 (26.6)	78 (40.0)	0.003
Smoke or drink	195 (48.0)	81 (41.5)	
Non-smoke and non-drink	103 (25.4)	36 (18.5)	
ART regimen group[*]			
PI/boosted PI	202 (49.8)	117 (60.0)	0.035
NNRTI	93 (22.9)	45 (23.1)	
INSTI	102 (25.1)	30 (15.4)	
NRTI sparing	9 (2.2)	3 (1.5)	
Comorbidities			
No	239 (58.9)	119 (61.0)	0.708
One	117 (28.8)	50 (25.6)	
Two or more	50 (12.3)	26 (13.3)	
Duration of ART prescription			
< 1 year	311 (76.6)	134 (68.7)	0.039
≥ 1 year	95 (23.4)	61 (31.3)	

[*] ART regimen group: antiretroviral treatment group, PI/boosted PI: Protease inhibitors/boosted protease inhibitors, NNRTI: Non-nucleoside reverse transcriptase inhibitors, INSTI: integrase standard transfer inhibitors, NRTI sparing: Nucleoside and nucleotide reverse transcriptase inhibitors sparing

Table 2
Factors associated with medication adherence by logistic regression analysis (n = 601).

Variable, (n)	Univariable logistic analysis c.OR	95 % CI	Multivariable logistic analysis a.OR	95 % CI
Depressive symptom				
Normal	Ref.		Ref.	
Depression	0.59	0.40, 0.87	0.52	0.34, 0.79
Gender				
Male	Ref.		Ref.	
Female	1.32	0.62, 2.79	0.87	0.38, 1.98
Age				
< 40	Ref.		Ref.	
40–59	1.00	0.70, 1.42	1.07	0.68, 1.70
≥ 60 years	2.70	1.22, 5.98	3.32	1.30, 8.54
Exposure category for HIV infection				
Homosexual	Ref.		Ref.	
Heterosexual	1.36	0.92, 2.03	1.27	0.81, 2.00
Bisexual	0.87	0.56, 1.36	0.86	0.54, 1.38
Marital status				
Unmarried	Ref.		Ref.	
Married	1.46	0.96, 2.21	1.16	0.68, 2.00
Divorced etc.	1.11	0.67, 1.84	1.10	0.59, 2.05
Health-related factor				
Smoke and drink	Ref.		Ref.	
Smoke or drink	1.74	1.18, 2.57	1.63	1.09, 2.46
Non-smoke and non-drink	2.07	1.28, 3.33	1.75	1.05, 2.90
ART regimen group[*]				
PI/boosted PI	Ref.		Ref.	
NNRTI	1.20	0.78, 1.83	1.23	0.79, 1.92
INSTI	1.97	1.24, 3.14	1.97	1.20, 3.25
NRTI sparing	1.74	0.46, 6.55	1.94	0.49, 7.59
Comorbidities				
No	Ref.		Ref.	
One	1.17	0.78, 1.73	1.18	0.77, 1.83
Two or more	0.96	0.57, 1.61	0.98	0.54, 1.78
Duration of ART prescription				
< 1 year	Ref.		Ref.	
≥ 1 year	0.67	0.46, 0.98	0.67	0.44, 1.01

[*] ART regimen group: antiretroviral treatment group, PI/boosted PI: Protease inhibitors/boosted protease inhibitors, NNRTI: Non-nucleoside reverse transcriptase inhibitors, INSTI: integrase standard transfer inhibitors, NRTI sparing: Nucleoside and nucleotide reverse transcriptase inhibitors sparing

being administered INSTI was only 3.5 % (14/401) of participants at registration. After four years, this had increased to 29.4 % (106/361).

In total, longitudinal data results including 1323 observations from 466 patients for the panel regression analysis are presented in Table 3. The negative impact of depression on medication adherence was estimated (a.OR = 0.50, 95 % CI 0.30, 0.84, p = 0.009). The non-smoking and non-drinking participants were 2.31 times more likely to adhere than those who smoked and drank (95 % CI 1.29, 4.15, p = 0.005). The odds ratio of ≥ 1 year of prior ART prescription at cohort enrollment was 0.37 (95 % CI 0.21, 0.65, p = 0.001). There were no significant differences in participants' medication adherence by gender, marital status, and exposure category for HIV infection.

Discussion

The findings of the current study demonstrated a significant negative association between depression and optimal ART medication adherence in PLWH using both cross-sectional and longitudinal panel data analyses. The study also revealed that INSTI-based ART regimens had a positive impact on medication adherence in the cross-sectional analysis. The introduction of Single Tablet Regimen (STR) consisting of INSTI and 2NRTIs reduced the complexity of ART prescription, resulting in improved medication adherence among PLWH [24]. However, in the longitudinal panel data analysis, this effect was not statistically significant. Our study identified that depression is associated with lower adherence, and a healthy lifestyle, such as, not smoking and not drinking, influenced medication adherence over time.

These findings are consistent with previous studies that have shown that depression is a critical mental health barrier to managing highly active antiretroviral treatment (HAART) medication adherence [25–27]. A Vietnam study has demonstrated that depressive symptoms are associated with suboptimal ART adherence. The odds ratio showed that depressive symptoms are 3.26 × higher in individuals with sub-optimal adherence [28]. Longitudinal studies from other countries have reported the factors influencing HAART adherence. HAART adherence is affected over time and is dependent on the sociodemographic factors (i.e., gender, education), emotional supports (i.e., depression, anxiety), and behavioral characteristics of the patients [29,30]. A previous Korean study has suggested that patients with depression are more likely to frequently forget outpatient clinical visits when compared with patients without depression [15]. A longitudinal association between depression and ART adherence has not been fully evaluated. Nonetheless, results of our longitudinal panel regression analysis demonstrated the relationship between depression and medication adherence over time.

There are several limitations in this research. First, the panel dataset we used is a sample of some of the participating hospitals in the KoCosHIV; therefore, it may not be representative of the general population of individuals living with HIV/AIDS in Korea. However,

Table 3
Factors associated with medication adherence by panel regression model (1323 observations from n = 466).

Variables	Odds ratio	95 % CI	p-value
Depressive symptom			
Depression	0.50	0.30, 0.84	0.009
Gender			
Female	0.53	0.17, 1.60	0.257
Age	1.05	1.02, 1.08	0.001
Exposure category for HIV infection			
Homosexual	Ref.	Ref.	
Heterosexual	1.19	0.62, 2.28	0.606
Bisexual	0.73	0.37, 1.42	0.350
Marital status			
Unmarried	Ref.	Ref.	
Married	0.84	0.39, 1.80	0.659
Divorced etc.	0.81	0.35, 1.88	0.622
Health-related factor			
Smoke and drink	Ref.	Ref.	
Smoke or drink	1.64	0.99, 2.72	0.051
Non-smoke and non-drink	2.31	1.29, 4.15	0.005
ART regimen group[*]			
Boosted PI	Ref.	Ref.	
Non-boosted PI	1.67	0.80, 3.49	0.171
NNRTI	1.16	0.67, 2.03	0.595
INSTI	1.88	0.98, 3.60	0.057
NRTI sparing	0.62	0.18, 2.08	0.435
Comorbidities			
No	Ref.	Ref.	
One	1.32	0.80, 2.16	0.276
Two more	1.34	0.60, 2.98	0.475
Duration of ART prescription			
< 1 year	Ref.	Ref.	
≥ 1 year	0.37	0.21, 0.65	0.001

[*] ART regimen group: antiretroviral treatment group, PI/boosted PI: Protease inhibitors/boosted protease inhibitors, NNRTI: Non-nucleoside reverse transcriptase inhibitors, INSTI: integrase standard transfer inhibitors, NRTI sparing: Nucleoside and nucleotide reverse transcriptase inhibitors sparing

the results have been obtained from representative general hospitals across the country; also, the 21 hospitals participating in the study consisted of 4 general hospitals and 17 tertiary general hospitals. Seventeen out of 45 tertiary general hospitals designated every three years by Korea government to efficiently utilize medical services were included. Second, the outcome measures of ART adherence are based on self-reported responses during the last 6 months; therefore, they may be subject to recall and social desirability biases. Nonetheless, Osterberg et al. have recommended that these self-reports are a suitable method to measure medication adherence. Moreover, most studies assessing medication adherence collect data on adherence scales through a self-reported questionnaire [31]. Third, the cut-off points for depression were determined using a BDI score ≥ 21 or EQ-5D anxiety/depression domain ≥level 2. In the KoCosHIV, BDI was repeatedly measured every year before 2015; however, due to the substitution by EQ-5D after 2015, depression as an explanatory variable had to be a combined BDI score with the anxiety/depression domain in EQ-5D. Fourth, information on psychiatric counseling or medication was lacking in our data. However, we used longitudinal panel data with annual surveys of depression (indicated by BDI scores or EQ-5D scores) and medication adherence. Therefore, we can assume any past treatment of depression was accounted for in the analysis through the present depression score. While we were unable to collect information on psychiatric treatments, this longitudinal panel analysis partially mitigated the limitations of the available data.

Our study has various merits. To the best of our knowledge, it is the first to examine the relationship between depression and ART adherence that accounts for confounders of the association with medication adherence using a longitudinal analysis model. Moreover, we assessed the interaction between depression and medication adherence based on panel regression analysis. Our results suggest that depression had a negative influence on medication adherence even after long follow-up period. Finally, the KoCosHIV is the largest study in Korea on the mental health of PLWH and ART adherence to use validated epidemiological data. We have estimated the effect between depression and ART adherence by using reliable data from the Korea Disease Control and Prevention Agency.

Conclusion

Our finding has identified depression and lifestyle modifications, such as non-smoking and non-drinking, as significant contributors to medication adherence. These findings emphasize the importance of proactive interventions to focus on supporting individuals with depressive symptoms and promoting medication adherence. Additionally, it is crucial to provide intensive monitoring for PLWH with more severe depressive symptoms, including those experiencing suicidal ideation. These interventions should be implemented not only during the initial diagnosis of HIV/AIDS patients but also throughout the maintenance phase of antiretroviral treatment. Based on this research, it is imperative to continue providing psychological counseling and programs to optimize the treatment outcomes of PLWH.

Ethical approval

Ethical approval was obtained from KDCA Institutional Review Board Ethics Committee. An informed consent waiver to manage retrospective data was approved by the Institutional Review Board of Yonsei-university (7001988-202012-HR-1073-01E).

Authors Contributions

KSO and EH designed the model and the framework. KSO analyzed the data. KSO wrote the manuscript with input from all authors (HCK, HYK, JYL, and JSL). EH was in charge of overall direction and planning.

Declaration of Competing Interest

There is no conflict of interest to declare.

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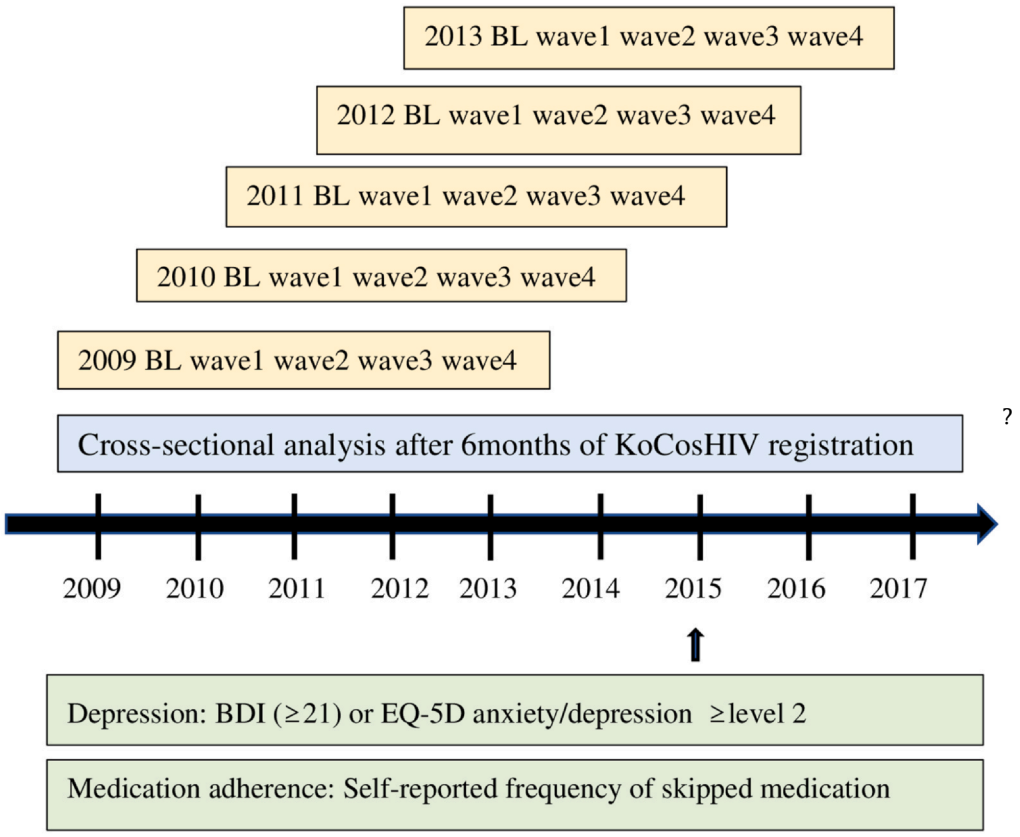
Korea HIV/AIDS Cohort Study

Sites: Ajou University Hospital, Asan Medical Center, Chungbuk National University Hospital, Ewha Womans University Mokdong Hospital, Gacheon University Gil Medical Center, Hallym University Kangdong Sacred Heart Hospital, Hallym University Kangnam Sacred Heart Hospital, Hallym University Sacred Heart Hospital, Hanyang University Seoul Hospital, Inha University Hospital, Kangbuk Samsung Hospital, Korea University Anam Hospital, Korea University Ansan Hospital, Korea University Guro Hospital, Kyungpook National University Hospital, Soonchunhyang University Seoul Hospital, The Catholic University of Korea, Seoul ST. Mary's Hospital, The Catholic University of Korea, ST. Vincent's Hospital, Yeungnam University Medical Center, Yonsei University Severance Hopital, Yonsei University Wonju Severance Christian Hospital.

Data center: Department of Preventive Medicine, College of Medicine, Hanyang University.

Appendix 1. Conceptual framework of the panel data analysis



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Appendix 2. Conceptual framework of the panel data analysis

Variable	Baseline (n = 515)	Wave 1 (n = 496)	Wave 2 (n = 412)	Wave 3 (n = 392)	Wave 4 (n = 381)	p-value
Gender						
Male	482 (93.6)	464 (93.6)	391 (94.9)	366 (93.4)	356 (93.4)	0.886
Female	33 (6.4)	32 (6.5)	21 (5.1)	26 (6.6)	25 (6.6)	
Exposure category for HIV infection						
Homosexual	169 (33.7)	161 (33.4)	137 (33.8)	128 (33.2)	120 (32.0)	0.999
Heterosexual	203 (40.5)	197 (40.9)	162 (40.0)	160 (41.5)	157 (41.9)	
Bisexual	129 (25.8)	124 (25.7)	106 (26.2)	98 (25.4)	98 (26.1)	
Marital status						
Unmarried	296 (57.5)	249 (56.6)	221 (58.0)	208 (59.1)	184 (57.0)	0.994
Married	149 (28.9)	124 (28.2)	104 (27.3)	92 (26.1)	91 (28.2)	
Divorced etc.	70 (13.6)	67 (15.2)	56 (14.7)	52 (14.8)	48 (14.8)	
Age	42.6 ± 12.2	43.8 ± 12.3	44.6 ± 12.3	45.7 ± 12.4	46.4 ± 12.7	< 0.001
Medication adherence						
Non-adherence group	174 (37.9)	141 (35.9)	108 (30.2)	103 (30.6)	91 (29.3)	0.412
Adherence group	285 (62.1)	252 (64.1)	250 (69.8)	233 (69.4)	219 (70.7)	
Depression						
Normal	389 (75.5)	341 (82.8)	287 (83.0)	257 (80.8)	237 (78.7)	0.031
Depression	126 (24.5)	71 (17.2)	59 (17.0)	61 (19.2)	64 (21.3)	
Health-related factor						
Smoke and drink	151 (29.4)	126 (27.6)	117 (30.2)	117 (31.8)	116 (33.1)	0.760
Smoke or drink	200 (39.0)	190 (41.6)	153 (39.4)	147 (39.9)	140 (40.0)	
Non-smoke and non-drink	162 (31.6)	141 (30.8)	118 (30.4)	104 (28.3)	94 (26.9)	
*ART regimen group**						
Boosted PI	219 (54.6)	250 (53.9)	186 (47.0)	157 (42.2)	128 (35.4)	< 0.001
Non-boosted PI	39 (9.7)	51 (11.0)	46 (11.6)	41 (11.0)	39 (10.8)	
NNRTI	120 (29.9)	118 (25.4)	99 (25.0)	81 (21.8)	75 (20.8)	
INSTI	14 (3.5)	33 (7.1)	52 (13.1)	83 (22.3)	106 (29.4)	
NRTI sparing	9 (2.3)	12 (2.6)	13 (3.3)	10 (2.7)	13 (3.6)	
Comorbidities						
No	290 (58.0)	343 (84.9)	322 (85.2)	276 (78.4)	288 (84.7)	< 0.001
One	147 (29.4)	47 (11.6)	38 (10.0)	54 (15.3)	39 (11.5)	
Two more	63 (12.6)	14 (3.5)	18 (4.8)	22 (6.3)	13 (3.8)	

Duration of prior ART prescription						0.980
< 1 year	349 (67.8)	337 (67.9)	284 (68.9)	269 (68.6)	265 (69.6	
≥1 year	166 (32.2)	159 (32.1)	128 (31.1)	123 (31.4)	116 (30.4)	
Year of KoCosHIV Registration						0.934
2009	63 (12.2)	61 (12.3)	55 (13.4)	51 (13.0)	51 (13.4)	
2010	164 (31.9)	161 (32.5)	125 (30.3)	110 (28.1)	105 (27.6)	
2011	142 (27.6)	139 (28.0)	104 (25.2)	104 (26.5)	104 (27.3)	
2012	99 (19.2)	89 (17.9)	85 (20.6)	90 (23.0)	86 (22.6)	
2013	47 (9.1)	46 (9.3)	43 (10.5)	37 (9.4)	35 (9.2)	

*ART regimen group: antiretroviral treatment group, PI/boosted PI: Protease inhibitors/boosted protease inhibitors, NNRTI: Non-nucleoside reverse transcriptase inhibitors, INSTI: integrase standard transfer inhibitors, NRTI sparing: Nucleoside and nucleotide reverse transcriptase inhibitors sparing

Appendix 3. Antiretroviral medication list used Korea HIV/AIDS Cohort Study

ATC code	Drug name	Approval	Antiretroviral treatment category
J05AF01	Zidovudine	1987	NRTI
J05AF02	Didanosine	1991	NRTI
J05AF03	Zalcitabine	1992	NRTI
J05AF04	Stavudine	1994	NRTI
`	Saquinavir	1995	PI
J05AF05	Lamivudine	1995	NRTI
J05AE02	Indinavir	1996	PI
J05AE03	Ritonavir	1996	PI
J05AG01	Nevirapine	1996	NNRTI
J05AE04	Nelfinavir	1997	PI
J05AG02	Delavirdine	1997	NNRTI
J05AR01	Lamivudine+Zidovudine	1997	NRTI
J05AF06	Abacavir	1998	NRTI
`	Efavirenz	1998	NNRTI
J05AE05	Amprenavir	1999	PI
J05AR05	Ritonavir + Lopinavir	2000	PI + Pharmacokinetic Enhancer
J05AF07	Tenofovir	2001	NRTI
J05AE07	Fosamprenavir	2003	PI
J05AE08	Atazanavir	2003	PI
J05AF09	Emtricitabine	2003	NRTI
J05AX07	Enfuvirtide	2003	Fusion inhibitor
J05AR02	Lamivudine + Abacavir	2004	NRTI
J05AR03	Tenofovir disoproxil + Emtricitabine	2004	NRTI
J05AE10	Darunavir	2006	PI
J05AJ01	Raltegravir	2007	INSTI
J05AX09	Maraviroc	2007	CCR5 receptor antagonist
J05AG04	Etravirine	2008	NNRTI
J05AG05	Rilpivirine	2011	NNRTI
J05AR04	Elvitegravir+Tenofovir disoproxil+Emtricitabine+Cobicistat	2012	Combination Drugs
J05AJ03	Dolutegravir	2013	INSTI
J05AJ02	Elvitegravir	2014	INSTI
J05AR06	Dolutegravir+Lamivudine+Abacavir	2014	Combination Drugs
ATC code	Drug name	Approval	Antiretroviral treatment category
J05AR07	Darunavir + Cobicistat	2015	PI + Pharmacokinetic Enhancer
J05AR08	Atazanavir + Cobicistat	2015	PI + Pharmacokinetic Enhancer
J05AR10	Elvitegravir+Tenofovir alafenamide+Emtricitabine+Cobicistat	2015	Combination Drugs
J05AR09	Tenofovir alafenamide + Emtricitabine	2016	NRTI

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