

Causes of HIV Drug Non-Adherence in Korea: Korea HIV/AIDS Cohort Study, 2006-2015

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We aimed to determine the initial adherence of HIV cohort patients to ART (antiretroviral therapy), and reasons for non-adherence. Patients who received ART at the time of enrollment in the Korea HIV/AIDS Cohort were included in this study. Treatment adherence was determined at the baseline interview by self-reported questionnaire. Eight-hundred thirty two HIV-infected patients received ART. Of these, 253 (30.4%) patients skipped ART more than once a month. The most common reason of skipping medication was “simply forgot” (60.4%).

Key Words: Human immunodeficiency virus; Cohort Study; Adherence

Because of the effectiveness of antiretroviral drugs, adequate adherence to medication is an important factor in the success of antiretroviral therapy (ART). Many previous studies showed that poor adherence to medication led to failure of viral suppression and poor recovery of CD4+ T cells [1, 2]. Poor adherence causes low CD4+ cell levels and low CD4+ cell levels are obviously associated with opportunistic infections [3]. In addition,

treatment failure due to poor adherence can mislead physicians, resulting in an unnecessary change of ART [4]. Causes affecting adherence have been studied in other countries [5]. In Korea, some studies have examined adherence to medication in HIV-infected patients, but a limited population was studied [6-8]. Thus, we evaluated the degree of adherence to medication and causes of non-adherence in Korea using the

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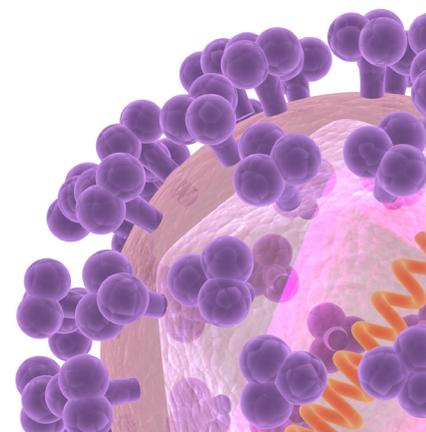
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Korea Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) Cohort data.

The Korea HIV/AIDS Cohort Study was initiated in 2006, and is a prospective observational study in South Korea. HIV-infected patients older than 18 years were registered the cohort after obtaining informed consent. Trained study nurses with supervision of infectious diseases physicians from all hospitals collected information every 6 month, using standardized survey form. The survey form of the cohort study is divided into six categories and consists of about 270 items; socioeconomic status, medical history, information of HIV/AIDS infection and treatment, opportunistic infection, physical findings, and laboratory results including virological and immunological status. In the category of HIV/AIDS infection and treatment, the information included history of HIV infection, presence of HIV relating/defining diseases, history of antiretroviral therapy, mutation of antiretroviral drugs, and treatment adherence in the most recent 3 months. The treatment adherence consists of four questionnaires; current ART prescription status, frequency of skipping ART, reasons of skipping ART (multiple responses), and ranking of reasons for skipping ART. Institutional review board approval was obtained from all participating hospitals.

In this study, using the baseline data of the Korea HIV/AIDS cohort at the time of enrollment, we investigated the treatment adherence, from December 2006 to October 2015. In the cohort patients, we included the patients receiving ART at the time of enrollment. We investigated frequency of skipping antiretroviral drugs. And we divided into the two groups by frequency of skipping; one group is patients taking ART without skipping, and the other who were taking medicine with skipping more than one time or did not answer specific response. Except for patients taking ART without skipping, study patients researched reasons for skipping medicine and self-ranking of the reasons. Student's *t*-test or the Wilcoxon rank-sum test was used to analyze continuous variables, and the Chi-square test or Fisher exact test was used for categorical variables. Statistical analyses were performed using R statistics ver. 3.2.1, and $P < 0.05$ was considered statistically significant.

A total of 1,356 HIV-infected patients were enrolled in the cohort study. Of these, 832 (61.4%) received ART at the time of enrollment in the cohort. The number of male and female patients were 778 (93.5%) and 54 (6.5%), respectively. Of the 832 patients, 537 (64.5%) were taking medicine without skipping medicine. Other 253 (30.4%) patient skipped ART more than one time. And, 42 (5.1%) patients did not give specific answer to the questionnaires. Table 1 shows the baseline characteris-

tics of study population. Median age was 43 years (interquartile range [IQR], 34-51) Median value of CD4+ T cell count was 385 cells/mm³ (IQR, 235-552) and the median value of HIV-RNA titer was 28 copies/mL (IQR, 19-137.5). Six hundred seventy-one patients took medicine twice a day. The median number of tablets per day was 5 (IQR, 3-7) (Table 1).

Table 2 shows the frequency of skipping. The most reported frequency of skipping was once a month, in 108 patients (108/832, 12.98%). The next most reported frequency was once a week (50/832, 6.01%). The reasons for skipping ART are presented in Table 3. "Simply forgot" was the most common reason (177, 60.4% of respondents). Side effects of antiretroviral drugs were reported second most common reason (24, 8.1%). Other reasons for skipping included being away from home, not eating a meal, fear of revealing the diagnosis to others, drinking alcohol, being busy, misinformation about ART, missing a visit to the outpatient clinic, poor economic status, lack of motivation, too many pills, other acute illness, and herbal medication. Forty-one patients did not give specific answer to this question (14.0%) (Table 3). In the result of the ranking of reasons for skipping ART, question to know the importance of each reason to skip medication, "Simply forgot" was the highest ranked reason (168/295, 56.9%), followed by side effects of antiretroviral drugs (18/295, 6.1%).

We conducted an analysis according to age group. In all age groups, "simply forgot" was the most common reason. In the 20s and 30s groups, fear of revealing the diagnosis was the second most common reason: 4 in their 20s (4/38, 10.5%) and 8 in their 30s (8/93, 8.6%). In the 40s group, a side effect was the second most common reason (10/92, 10.9%). Being away from home including travel was the second most frequently reported reason in the 50s and 60s groups: 5 in their 50s (5/55, 9.1%) and 4 in their 60s (4/16, 25%).

Achieving a high level of adherence is important in the management of any chronic disease. In HIV/AIDS, good adherence is equally critical for long-term viral suppression. Studies of treatment adherence have been conducted in various countries. The Adult AIDS Clinical Trials Group (AACTG) reported that 63% of 93 enrolled patients showed >95% adherence [2]. In China, 80.7% of patients took all antiretroviral drugs, and those with adherence rates of 95-99% and 90-94% accounted for 15.5% and 1.9%, respectively [9]. A meta-analysis evaluated 84 observational studies performed in 20 countries, and found that 62% reported $\geq 90\%$ ART adherence [10]. One report evaluated adherence in Korea. In this study, 53.1% of patients (26 of 49) reported regular adherence to antiretroviral drugs [7]. In our study, 64.5% of patients took medicine every day, without

Table 1. Baseline characteristics of study population

Characteristic	Total (n = 790)	Skipping ART (-) (n = 537)	Skipping ART (+) (n = 253)	P-value
Median age, yr	43 (34-51)	44 (34-53)	42 (34-49)	0.038
Male				0.134
MSM	211 (26.7)	137 (25.5)	74 (29.2)	
MSW	287 (36.3)	194 (36.1)	93 (36.8)	
Bisexual man	59 (7.5)	35 (6.5)	24 (9.5)	
Female	51 (6.5)	40 (7.4)	11 (4.3)	0.134
Marriage status				0.039
Single	421 (53.3)	269 (50.1)	152 (60.1)	
Married	214 (27.1)	155 (28.9)	59 (23.3)	
Separation	15 (1.9)	10 (1.9)	5 (2.0)	
Divorce	69 (8.7)	45 (8.4)	24 (9.5)	
Bereavement	12 (1.5)	8 (1.5)	4 (1.6)	
Cohabitation	11 (1.4)	10 (1.9)	1 (0.4)	
Smoking, current	329 (41.6)	195 (36.3)	134 (53.0)	<0.0001
Alcohol, current	370 (46.8)	222 (41.3)	148 (58.5)	<0.0001
Underlying diseases				
Diabetes ^a	45 (5.8, 9)	29 (5.5, 5)	16 (6.4, 4)	0.747
Dyslipidemia ^a	106 (13.7, 22)	58 (11, 10)	48 (19.4, 12)	0.002
Metabolic syndrome ^a	3 (0.4, 2)	1 (0.2, 1)	2 (0.8, 1)	0.507
Lipodystrophy ^a	27 (3.4, 25)	20 (3.8, 20)	7 (2.8, 5)	0.621
Osteoporosis ^a	7 (0.9, 2)	3 (0.6, 2)	4 (1.6, 0)	0.309
Hypertension ^a	80 (10.3, 16)	52 (9.9, 11)	28 (11.1, 5)	0.683
Myocardial Infarction	4 (0.5)	2 (0.4)	2 (0.8)	0.817
Angina	4 (0.5)	2 (0.4)	2 (0.8)	0.817
Cerebral Infarction	6 (0.8)	6 (1.1)	0 (0)	0.210
Cerebral hemorrhage	3 (0.4)	1 (0.2)	2 (0.8)	0.506
Hepatitis B ^a	39 (5.0, 15)	27 (5.1, 10)	12 (4.8, 5)	0.976
Hepatitis C ^a	9 (1.1, 3)	6 (1.1, 3)	3 (1.2, 0)	1.000
Fatty liver	13 (1.7)	9 (1.7)	4 (1.6)	1.000
Liver cirrhosis	7 (0.9)	3 (0.6)	4 (1.6)	0.309
CKD with HD	1 (0.1)	0 (0)	1 (0.4)	0.702
CKD with PD	1 (0.1)	0 (0)	1 (0.4)	0.702
Median CD4+ T cell count (cells/mm ³)	385 (235-552)	384 (225-552)	392 (254-553)	0.339
Median HIV-RNA (copies/mL)	28 (19-137.5)	30 (19-150)	25 (19-131)	0.936
Opportunistic infection ^b	232 (29.4)	150 (27.9)	82 (32.4)	0.228
Prophylaxis of opportunistic infection ^b	106 (13.4)	75 (14.0)	31 (12.3)	0.584
ART regimen				0.355
PI	70 (8.9)	45 (8.5)	25 (10.0)	
Boosted PI	394 (50.3)	258 (48.5)	136 (54.2)	
NNRTI	234 (29.9)	165 (31.0)	69 (27.5)	
NRTI	4 (0.5)	4 (0.8)	0 (0)	
INI	66 (8.4)	49 (9.2)	17 (6.8)	
Others	15 (1.9)	11 (2.1)	4 (1.6)	
Number of tablets/day	5 (3-7)	5 (3-7)	5 (3-7)	0.612
Number of daily doses				0.018
1 times/day	99 (12.6)	79 (14.8)	20 (8.0)	
2 times/day	671 (85.7)	443 (83.3)	228 (90.8)	
3 times/day	13 (1.7)	10 (1.9)	3 (1.2)	
Past ART history	444 (56.2)	267 (49.7)	177 (70.0)	<0.0001
Number of past ART regimen	2 (1-3)	1 (1-3)	2 (1-3)	0.023
Experience of treatment failure	54 (12.2)	25 (9.4)	29 (16.4)	0.039
Median duration of current ART (day)	226.5 (68-541)	212 (60-523)	259.0 (98-546)	0.047
Median duration of total ART (day)	516.5 (149-1,331)	395 (96.5-1,049.0)	784 (298.5-1,952)	<0.0001

Values are presented as number (%) or median (interquartile range).

^aThese values are percentage and the number of patients being treated.

^bOpportunistic infection included *Pneumocystis jirovecii* infection, *Toxoplasma gondii* infection, *Candida* infection *Cryptococcus neoformans* infection, *Salmonella* infection, tuberculosis, and cytomegalovirus infection.

ART, antiretroviral therapy; MSM, men who have sex with men; MSW, men who have sex with women; CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis; HIV, human immunodeficiency virus; RNA, ribonucleic acid; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; INI, integrase inhibitor.

Table 2. Frequency of skipping antiretroviral drugs

Frequency of skipping antiretrovirals	Patients (%) ^a
Never once	537 (64.5)
Once a month	108 (13.0)
Once a week	50 (6.0)
Once in 2 weeks	43 (5.2)
No specific response	42 (5.0)
More than twice in one week	29 (3.6)
Daily	8 (1.0)
Once in 2-3 months ^b	7 (0.8)
Irregularity ^b	6 (0.7)
Others ^{b,c}	2 (0.2)

^aValues are presented as percentage of total study population (n=832).

^bThis frequency was answered by the respondents in free text.

^cThese patients skipped antiretroviral therapy for 25 days and 13 days, respectively.

skipping during the prior 3 months, and 108 were skipped ART only once a month. There was improvement in adherence compared to past reports. The rate of adherence was similar to that of other countries.

Results of questionnaire surveys investigating the reasons for non-adherence were similar in various studies. The AACTG and the Danish Cohort Study showed that simple forgetfulness was the most frequently reported reason for skipping ART [5, 11, 12]. Being away from home, change from daily routine, and being busy were also highly associated with skipping ART [5, 11, 12]. Other studies from Hong Kong, China, Costa Rica, and Italy showed similar results [9, 13-15]. Our study found that “simply forgot” was the most common self-reported reason for skipping ART, which is consistent with the findings of previous studies. However, a side effect was the second most common reason given for skipping ART, and was ranked higher than in other studies. Other reasons given were similar to those from other countries. Pill numbers and side effects were factors related to the antiretroviral drug itself. Otherwise, most items reflected lack of understanding of the disease. We should promote adherence through education and counseling. In our study, the most common reason given for skipping ART was “simply forgot” in all age groups. However, the next most frequent reason was different in each age group. Therefore, tailored individual counseling should be performed for successful treatment.

A change in adherence over time was reported by the AIDS Clinical Trials Group (ACTG) and the Royal Free Clinic Cohort [2, 16]. Their results did not show a similar trend. The ACTG

Table 3. Reasons for skipping antiretroviral therapy (multiple responses)

Reasons	Frequency (%) ^a
Simply forgot	177 (60.4)
No specific response	41 (14.0)
Side effects of antiretroviral drugs	24 (8.1)
Being away from home	22 (7.5)
Not eating a meal	18 (6.1)
Fear of revealing diagnosis to others	17 (5.8)
Drinking alcohol	17 (5.8)
Busy	9 (3.1)
Misinformation about ART	5 (1.7)
Missing a visit to outpatient clinic ^b	4 (1.4)
Low socioeconomic status	3 (1.0)
Lack of motivation ^b	3 (1.0)
Other acute illness ^b	3 (1.0)
Too many pills	3 (1.0)
Herbal medication ^b	1 (0.3)
Total	347

^aValues are presented as percentage of respondents (n = 295).

^bThese were answered by the respondents in free text.

ART, antiretroviral therapy.

assessed adherence every 4 weeks until week 24. The adherence rate decreased over time [2]. The Royal Free Clinic Cohort assessed adherence every 6 months. Adherence slightly increased over time [16]. The Korea HIV/AIDS Cohort Study investigated the data for each 6-month period. We reviewed the initial data at the time of patient enrollment. It is necessary to understand the long-term trend in adherence by Korean HIV-infected patients. Therefore, additional analysis will be needed using follow-up data.

In our study, a substantial portion of responses to each question was “no specific response”. Unlike other reports, the side effects of antiretroviral drugs were the second most common reasons for skipping ART. Side effects should be an important factor in Korea. However, being busy or a change in daily schedule, which were frequently reported reasons in other countries, might be underestimated by “no specific response”. This was a limitation of the self-reported questionnaire. Moreover, median value of HIV-RNA titer was low level, which showed no difference between patients group who skipped drug more than one time and the other group. Patients participating in the cohort were likely to be cooperative with the physicians. It was estimated that most cohort populations have low viral load. Therefore, we thought that ‘simply forgot’ did

not reach clinical significance in this study population. We thought that the cohort population did not fully reflect the treated Korea HIV-infected patients, which was considered a limitation in the interpretation of this study. Nevertheless, we think that our study data will aid in the understanding of treatment adherence and contributory factors in Korean HIV-infected patients.

In conclusion, among the Korea HIV/AIDS cohort, about 30% of patients skipped antiretroviral drug more than once a month. The most common reason of skipping medication was “simply forgot”.

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Conflicts of Interest

No conflicts of interest.

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