Non-adherence to Anti-retroviral Therapy among HIV-Infected Individuals in Kyrgyzstan: Prevalence and Risk Factors, 2014-2016

Aisuluu Kubatova, Aizat Arunova, U. K. Kadyrbekov and Simon Ajeilat
1. National AIDS Center, Ministry of Health, Street Logvinenko 8, Bishkek 720001, Kyrgyz Republic
2. Department of Disease Prevention and State Sanitary Epidemiologic Surveillance, Ministry of Health, Street Razzakova 63, Bishkek, Kyrgyz Republic
3. National AIDS Center, Ministry of Health, Street Logvinenko 8, Bishkek 720001, Kyrgyz Republic
4. Central Asia Field Epidemiology Training Program

Abstract: Backgrounds: Currently in Kyrgyzstan, ART (antiretroviral therapy) is freely provided to HIV-infected individuals on clinical grounds. Strict adherence to ART is required, it improves HIV-infected individuals’ survival and quality of life, prevents HIV transmission and drug resistance. Our study aims to identify the prevalence of non-adherence to ART therapy and factors associated with it so that strategies can be designed to help maintain adherence. Methods: In a retrospective cohort study, we enrolled randomly selected 432 individuals, ≥ 18 years of age, from among all HIV-infected individuals in Kyrgyzstan (n = 950) who started ART during Jan. 2014-Sep. 2016. All were followed up until Dec. 2016. Non-adherents were: (1) individuals lost to follow-up; (2) individuals who missed ≥ 4.5 days of treatment per 30 days during the study period—this was established by comparing the total tablets prescribed, dates of visits for treatment, and number of tablets consumed. We reviewed the country’s HIV surveillance data and medical facilities records. We collected information on the known non-adherent risk factors, HIV clinical presentation, and details of treatment-regimens. We used logistic regression to assess the risk factors and non-adherent associations. Results: The overall non-adherence rate was 50% (214/432). In sub-group analysis, the highest rate was: 61% (50/82) among alcohol abusers, 60% (65/109) in those who received ≥ 2 tablets/dose, 59% (44/75) in those receiving ≥ 2 doses/day, 57% (89/155) in drug users, and 53% (144/271) in individuals aged < 40 years. In multivariate analysis, ≥ 2 tablets/dose (OR = 2.1, 95% CI 1.0-4.1), age < 40 years (OR = 1.7, 95% CI 1.1-2.6), and alcohol abuse (OR = 1.6, 95% CI 1.0-2.8) were associated with non-adherence. Conclusion: The observed non-adherence rate is unacceptably high. Adherence can be improved by introducing the one tablet/day treatment regimen, establishing regular contact with those under ART, and providing them with appropriate counseling, especially those < 40 years of age or with substance abuse.

Key words: HIV, non-adherence, antiretroviral therapy, Kyrgyzstan.

1. Introduction

ART (antiretroviral therapy) is an effective measure for treatment and prevention of HIV (human immunodeficiency virus) and requires intake of medications with adherence to treatment regimen over one’s life [1, 2]. In the last decade the WHO (World Health Organization) has been focusing on expanding ART coverage and developing principles, tools and training materials, which allow the primary and secondary care facilities to provide HIV prevention, treatment, and use standardized patient tracking form Ref. [3]. According to a study, done in 2013 in the USA, life expectancy with ART among HIV-positive people was up to 70 years, which almost equals life expectancy without HIV [1]. It was also proven that ART compliance reduces sexual transmission of HIV by 92% [4]. According to the WHO recommendations, adherence to ART should be no less than 95%. As a result of such adherence, mortality indicators can be
Reduced, HIV transmission to other people can be prevented, and HIV-associated infections and resistant strains of HIV can be prevented [5, 6]. According to Refs. [7, 8], non-adherence risk factors were subdivided into 5 main groups: social and demographic factors, treatment regimen-related factors, diseases characteristics and progression, patient-physician relations, as well as public health aspects, including access to primary care. Other non-adherence risk factors are low awareness about health matters, age-related issues (for instance polymedication, sight loss, cognitive impairments), young age, psycho-social problems (depression, homelessness, low social support, stressful events or psychosis) [7, 8]. According to the results of another study, non-adherence factors include forgetfulness about taking medications, tight medication schedule, hiding HIV-status from close ones and medication side-effects [6]. In fact, low adherence is the second top cause of death among adolescents globally and top cause of death of adolescents in Africa [9].

As of beginning of 2017, KR (Kyrgyz Republic) was experiencing concentrated epidemics stage of HIV with 7,117 cases of HIV registered on Jan. 01, 2017. Estimated number of people, living with HIV (PLH) in 2016 was 8,500 people. ART was prescribed to 3,609 patients, of which 2,668 PLHs receive therapy [10].

ART has been provided free of charge in KR since March 2005. According to clinical protocol of 2015, treatment was ordered by clinical indications. A new clinical protocol was adopted in 2017, according to which treatment is prescribed, when HIV is diagnosed.

KR has an electronic HIV cases tracking system since 2012, which includes the following patient records: clinical, epidemiologic, laboratory and therapy adherence assessment. ART is provided in AIDS centers, and in remote regions, in family medicine centers have ART logs. According to the clinical protocol, adherence ART assessment is calculated using the formula:

\[(N_g - N_r)/N_m \times 100\%
\]

- \(N_g\)—number of tablets given;
- \(N_r\)—number of tablets remaining;
- \(N_m\)—number of tablets the patient has to take.

According to the clinical protocol of 2015, adherence in KR is assessed after 1 month of ART on the basis of calculating expected and actual number of medications taken. Treating physician conducts the assessment by asking questions, and viral load is used as the control. Treating physician assesses adherence on a monthly basis, counts the number of tablets given, asks patient about residual tablets and calculates adherence, using the formula [11]. The data of assessment are included into electronic tracking system quarterly.

Right now, there are data on quality of conducting adherence assessment, but according to the data from Electronic HIV case tracking system, adherence level in the country reaches 84.8%, with the lowest levels in Talas (50%) and Chu (59%) regions in 2015 (Table 1). In 2016, the same picture was seen countrywide 83.7%, with the highest values in Issyk-Kul region, 100%.

This study was done with the purpose of identifying ART adherence level and factors, impeding development of ART adherence among HIV-positive patients, given their social, clinical and other peculiarities.

Table 1 Adherence to ARV-therapy in KR, electronic HIV case tracking system in 2015-2016.

| Region           | Adherence 2015 | Adherence 2016 |
|------------------|----------------|----------------|
| Naryn region     | 100%           | 86%            |
| Osh city         | 98%            | 89%            |
| Osh region       | 97%            | 90%            |
| Batkent region   | 91%            | 84%            |
| Bishkek          | 87%            | 81%            |
| Zh-Abad region   | 80%            | 94%            |
| Issyk-Kul region | 64%            | 100%           |
| Chu region       | 59%            | 71%            |
| Talass region    | 50%            | 86%            |
| KR               | 85%            | 84%            |
* Data from reporting form 4 health, RAC MH KR, 2015-2016.

2. Methods

2.1 Research Design

We have conducted retrospective cohort study. We have studied data of PLH aged 18 and above, who have started treatment in the period of January 2014 to August 2016, who received ARVs in AIDS centers and FMCs (family medicine centers) \((n = 432)\) until December 2016, selected randomly.

The sample included all PLHs receiving ART in the country, excluding pregnant women, children and people in penitentiary institutions, since we assumed that adherence in such cases may be different, and we needed to eliminate the mixing factors. We have used routine epidemiological surveillance data and other medical records in AIDS centers and FMC. We have gathered data from electronic HIV tracking system in KR and ART dispensing logs: social and demographic, clinical data, alcohol and drugs use, and date of ART receipt.

2.2 Calculations

There are several methods to track adherence, but for this study we used tablets counting [7]. Calculation of gaps in treatment was done by adding number of tablets received and comparison with number of ART days, using the following formula:

\[
gaps \text{ calculation} = \frac{\text{number of days of treatment} - \text{number of tablets given}}{\text{number of treatment days}} / 30
\]

Non-adhering patients were those, who have missed over 4.5 days of treatment over 30 days and who have interrupted ART.

2.3 Statistical Analysis

Data were transferred from paper form into EPI-INFO 7 data base, developed by the Centers for Disease Control and Prevention (CDC). The same software was used for data analysis.

To define the link between non-adherence and risk factors, logit regression was used. First, all variables were analyzed by single-factor analysis (ANOVA). Significance level was established at \(p = 0.05\), to eliminate mixing factors, variables with \(p\) lower than 0.1 \((p < 0.1)\) were included in the multi-factor logit model analysis.

2.4 Ethical Considerations

This study was done in the framework of 2-year training program in Applied Epidemiology in Central Asia FETP with support of National AIDS Center of the Ministry of Healthcare of KP. Routine HIV epidemiological surveillance data were used for analysis, no personal patient interviews were done. Personal data were removed to maintain confidentiality, and the report contained no personal data. Ethical approval for this study was waived by the ethics committee of the National AIDS Center since all data used in the study were collected as part of the routine surveillance and were de-identified prior to being analyzed by the researchers.

3. Results

Most participants of the study had secondary education (79.4%), denied alcohol consumption (81%) (Table 2). Most participants have been HIV-infected for less than 4 years (73.6%).

Out of 432 PLH, 214 (49.5%) did not adhere to ART (Table 3). We have analyzed 23 factors, of whom 9 factors had \(p\) less than 0.1 \((p < 0.1)\) and were included in the multi-factor logit model analysis.

3.1 Social and Demographic Factors

To analyze social and demographic factors epidemiological surveillance data were used (electronic tracking system): sex, age, education, employment. There are more non-adherent PLHs of age 40 and above—53% (144 of 271), male—53% (121 of 260), single—52% (129 of 267) and unemployed—50% (146 of 293).
### Table 2  Demographic characteristics of study participants.

| Factors           | Frequency (n = 432) | Percentage |
|-------------------|---------------------|------------|
| **Sex**           |                     |            |
| Female            | 172                 | 39.8       |
| Male              | 260                 | 60.2       |
| **Age group**     |                     |            |
| < 40 years        | 271                 | 62.7       |
| 40+ years         | 161                 | 37.3       |
| **Marital status**|                     |            |
| Married           | 165                 | 38.2       |
| Single            | 267                 | 61.8       |
| **Education level**|                    |            |
| Vocational, higher| 89                  | 20.6       |
| Secondary         | 343                 | 79.4       |
| **Employment**    |                     |            |
| Employed          | 139                 | 32.2       |
| Unemployed        | 293                 | 67.8       |
| **Alcohol consumption** |                |            |
| Drink alcohol     | 82                  | 19         |
| Do not drink alcohol | 350               | 81         |
| **Injected drug use** |                  |            |
| Use injected drugs| 155                 | 35.9       |
| Do not use injected drugs | 277       | 64.1       |
| **Duration of HIV infection** |                |            |
| < 4 years         | 318                 | 73.6       |
| 4+ years          | 114                 | 26.4       |
| **Length of HIV treatment** |              |            |
| < 1 year          | 211                 | 48.8       |
| 1+ year           | 221                 | 51.2       |
| **HIV stage**     |                     |            |
| 1-2 stage         | 250                 | 57.9       |
| 3-4 stage         | 182                 | 42.1       |

### Table 3  Demographic and behavioral correlations of non-adhering patients*.

| Factors                  | Adhering (n = 218; 50.5%) | Non-adhering (n = 214; 49.5%) | p-value |
|--------------------------|---------------------------|-------------------------------|---------|
| **Sex**                  |                           |                               |         |
| Female                   | 97 (56)                   | 75 (44)                       | 0.045   |
| Male                     | 121 (47)                  | 139 (53)                      |         |
| **Age group**            |                           |                               |         |
| < 40 years               | 127 (47)                  | 144 (53)                      | 0.053   |
| 40+ years                | 91 (57)                   | 70 (43)                       |         |
| **Marital status**       |                           |                               |         |
| Married                  | 89 (54)                   | 76 (46)                       | 0.256   |
| Single                   | 129 (48)                  | 138 (52)                      |         |
| **Education level**      |                           |                               |         |
| Vocational, higher       | 46 (52)                   | 43 (48)                       | 0.796   |
| Secondary                | 172 (50)                  | 171 (50)                      |         |
3.2 Behavioral Factors

To analyze behavioral factors, alcohol consumption and injected drug use were analyzed. The data were taken from epidemiological surveillance, interview about use of drugs and alcohol was done by local treating physician. There were more non-adherent patients, who consume alcohol—61 % (50 of 82) or use injected drugs—57% (66 of 89).

3.3 Clinical Factors

Data from epidemiological surveillance system were used to analyze clinical risk factors: stage of HIV infection, length of infection and length of HIV treatment. Dates of diagnosis and initiation of treatment were used for calculation. Non-adherence to therapy is seen among 54% (83 of 99) PLH with 3-4 clinical stages of HIV and 53.5% (113 of 211), who receive treatment for less than a year.

3.4 Medication or Treatment Scheme-Related Factors

Treatment scheme was used to analyze frequency of medication intake and number of tablets per dose. Furthermore, data on dates of dispensing and number of tablets were taken from the medication dispensing log. These data were used to calculate adherence. Non-adherence was seen among those who have more than 1 tablet per dose—59% (44 of 75) and more than 1 dose per day—60% (65 of 109). Non-adherence among patients, who have Zidovudine
(AZT) scheme, is 61% (40 of 66) (Table 4).

3.5 Side Effects

Among study participants of only 4.1% (18 of 432) have noticed side effects, and 15 of them were not adhering to treatment. The following side-effects were registered: headaches, dizziness, nausea, vomiting, hallucinations.

**Table 4  Contents of the prescribed schemes*.**

| Factors                  | Adhering (n = 218; 50.5%) | Non-adhering (n = 214; 49.5%) | p-value |
|--------------------------|---------------------------|-------------------------------|---------|
| Zidovudine (AZT) in scheme |                           |                               |         |
| No                       | 192 (52)                  | 174 (48)                      | 0.052   |
| Yes                      | 26 (39)                   | 40 (61)                       |         |
| Tenofovir (TDF) in scheme |                           |                               |         |
| No                       | 28 (42)                   | 39 (58)                       | 0.124   |
| Yes                      | 190 (52)                  | 175 (48)                      |         |
| Emtricitabine (FTC) in scheme |                         |                               |         |
| No                       | 29 (41)                   | 41 (59)                       | 0.100   |
| Yes                      | 189 (52)                  | 173 (48)                      |         |
| Lamivudine (3TC) in scheme |                          |                               |         |
| No                       | 189 (52)                  | 173 (48)                      | 0.100   |
| Yes                      | 29 (41)                   | 41 (59)                       |         |
| Abakavir (ABC) in scheme |                           |                               |         |
| No                       | 215 (51)                  | 209 (49)                      | 0.464   |
| Yes                      | 3 (38)                    | 5 (63)                        |         |
| Efavirenz (EFV) in scheme |                           |                               |         |
| No                       | 11 (37)                   | 19 (63)                       | 0.122   |
| Yes                      | 207 (51)                  | 195 (49)                      |         |
| Nevirapine (NVP) in scheme |                         |                               |         |
| No                       | 214 (50)                  | 210 (50)                      | 0.979   |
| Yes                      | 4 (50)                    | 4 (50)                        |         |
| Lopinavir (LPV) in scheme |                           |                               |         |
| No                       | 212 (51)                  | 205 (49)                      | 0.413   |
| Yes                      | 6 (40)                    | 9 (60)                        |         |
| Ritonavir (LPV/r) in scheme |                     |                               |         |
| No                       | 212 (51)                  | 205 (49)                      | 0.413   |
| Yes                      | 6 (40)                    | 9 (60)                        |         |

* Data analyzed in single-factor analysis.

**Table 5  Correlation between studied factors and low adherence (logistic regression analysis)*.**

| Risk factors                  | OR  | 95% CI |
|-------------------------------|-----|--------|
| Age < 40 years                | 1.7 | 1.1    |
| Male                          | 1.2 | 0.8    |
| Use of injected drugs         | 1.4 | 0.8    |
| Alcohol consumption           | 1.6 | 0.9    |
| More than 1 tablet per dose   | 2.1 | 1.0    |
| 2 doses per day               | 0.5 | 0.1    |
| Zidovudine (AZT)              | 1.8 | 0.4    |

* Data analyzed with multi-factor analysis.
With multi-factor analysis, the following were risk factors: age under 40 years (OR = 1.7; 95% CI 1.1-2.6), 2 or more tablets per single dose (OR = 2.1; 95% CI 1.0-4.1), and alcohol abuse (OR = 1.6; 95% CI 1.0-2.8) (Table 5).

4. Discussion

Adherence in the country is probably lower than official reported numbers, half of the sample had low adherence. PLHs, who take more than 1 tablet and more than 1 dose per day have low adherence to therapy, which can be explained by the fact that PLHs often forget to take medications. In terms of demographics, most non-adherent patients are of younger age, male, with secondary education, unemployed (do not work, do not study) and single. Furthermore, those who inject drugs or consume alcohol are less adherent to therapy. As a result of multi-factor analysis, young age (under 40 years), 2 or more tablets per dose, alcohol abuse are risk factors for low adherence to ART among PLH in KR. Verbal survey method is used in the country to check for residual tablets. In order to ensure continuous and reliable monitoring, other adherence assessment methods should be introduced, such as methods recommended by the WHO: viral load monitoring, clinical methods (tracking disease dynamics, complications, opportunistic infections), measuring medication of their metabolites concentrations, monitoring dynamics of mean cell volume (MCV), patient self-reporting and counting tablets in bottles [12].

Verbal survey method is considered one of the imprecise assessment methods due to “memory error” of the patient or psychological readiness to provide “expected answer” to the physician. To increase adherence to therapy it is necessary to introduce recommended methods (WHO): mutual consultations among PLHs, reminders in the form of messages, calendars etc., and trainings [12]. To provide incentives to the medical professionals to work on improving adherence, it is necessary to provide bonuses for ensuring patient adherence over 95%. According to the study results, we recommend to replace multi-tablet schemes by single tablet schemes and to strengthen consultative work on ART intake among PLHs under 40 years and those, who consume psychoactive substances.

5. Conclusions

According to the WHO recommendation, adherence to ART should be no less than 95%. As a result of such adherence levels, mortality and transmission of HIV to other people is reduced, HIV-associated infections and appearance of resistant strains of HIV are prevented. Main reasons for non-adherence, are forgetfulness about the intake of medications, tight medication schedule, hiding HIV status from close ones and side effects of medications.

According to our study, only half of the sample had good adherence. Furthermore, our study has demonstrated that young age, intake of more than 1 tablet per dose, alcohol abuse are risk factors for low adherence to ART.

To improve adherence to ART, it is necessary to work to create effective interventions.

6. Strengths and Limitations

Sample size and research design have guaranteed reliability and representativeness of our study. To assess adherence counting of dispensed tablets method was used, but one can not ignore the possibility that dispensed tablets were not taken. One of the limitations of the study was the use of epidemiological surveillance data, no personal interviews with the patients were done.

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