Adherence to Antiretroviral Therapy and Risk Factors Among MSM Patients in Hangzhou, China: A Cohort Study

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ABSTRACT

This cohort study was to assess levels of adherence to antiretroviral therapy and the risky factors among HIV-positive Men who have sexed with men (MSM) in Hangzhou, China in 2015-2017. HIV-positive MSM who were 18 years of age or older and went to the clinic to initiate ART between Jan 2015 and Jun 2016 were recruited. Data were collected at baseline and at follow-up times of 1, 6, 12 months. The Generalized Estimating Equations (GEE) model was used to examine the risk factors of adherence. Among 397 individuals, 82.6%, 80.9% and 79.9% were fully adherent to the treatment at 1, 6, 12 months of follow-up, respectively. In adjusted analyses, ART-initial CD4 cell count (<500 &≥500 cells/mm3) was not associated with ART adherence (Adjusted Risk Ratio [ARR]=0.765, 95%CI=0.476-1.230). Participants who were under 30 years of age and who used alcohol were associated with a higher risk of non-adherence (ARR=0.641, 1.809, 95%CI=0.441-0.931, 1.266-2.584). ART adherence was high among MSM as fellows. There was no effect of ART-initial CD4 cell count on adherence. Patients aged older and used alcohol need to be pay more attention.

Introduction

The prevalence of Human Immunodeficiency Virus (HIV) in Zhejiang province has increased substantially in the past three decades. The first case of HIV infection was reported in 1985 [1]. By the end of 2015, it was estimated that there was a cumulative total of 20,902 people living with HIV (PLWH) in Zhejiang province [2]. By the end of 2016, a total of 5,119 new HIV cases were reported in Zhejiang, and men who have sex with men (MSM) had the highest prevalence of HIV (6.92%). Hangzhou has been affected by the epidemic with an HIV prevalence of 8.5% among MSM [3-4]. Zhejiang province launched a Free Antiretroviral Treatment Program (FARTP) in 2003 and has scaled the program up rapidly since the initiation of China’s national FARTP in 2002. More than 90% of HIV/ Acquired Immune Deficiency Syndrome (AIDS) patients accepted anti-retroviral therapy (ART) if they were diagnosed by 2016 [5-7].

The introduction of ART decreases both the individual and community viral load, reducing mortality and morbidity in HIV-positive patients [8-10]. Furthermore, benefits have been reported for the early detection and early use of ART, such as a reduced risk of HIV transmission, better immune recovery, and lower chance of developing HIV-related diseases [11-12]. Successful treatment largely depends on patient adherence to the ART. Various factors affecting ART adherence have been identified. The principal factors associated with non-adherence appear to be patient-related factors
including alcohol and substance abuse [13]. One study has also stated other factors, such as pill burden and side-effects, depression, lack of family and social support, stigmatization and discrimination [14-15]. Despite the World Health Organization (WHO) guidance for early detection and early use of ART, assessing the benefits and drawbacks, such as side effects and long-term adherence, is always needed at the individual patient level. Few studies have discussed the impact of early ART-initial CD4 cell count on adherence, especially in developing countries.

The current study was undertaken by the infectious disease department in Xixi hospital in Hangzhou, Zhejiang province. All HIV/AIDS patients in Hangzhou are referred to the clinic to initiate the use of ART. Four full-time doctors and three nurses are available for treatment and follow-up. Our aim was to investigate the level of ART adherence and non-adherence among HIV-positive MSM in Hangzhou. We also evaluated the effect of early ART use on adherence over time while adjusting for other predictors.

### Materials and Methods

#### Study Population

The study was conducted at Xixi hospital in Hangzhou. Patients were enrolled if they met the following criteria: MSM, were 18 years of age or older, if they had sex with a male in the last year, and if they lived in Hangzhou for at least half a year. Patients who would not provide their informed consent were excluded from the study. Figure 1 shows the subject selection procedure.

![Study design flow chart for HIV/AIDS cohort study 2015-2016.](image-url)
Study Design

The study was a prospective cohort study in Zhejiang province with continued enrollment of HIV-positive patients from Jan 2015 to Jun 2016. The HIV/AIDS clinic of Xixi hospital of Hangzhou was in charge of study recruitment. Enrollment was conducted when patients went to the clinic to initiate ART. A total of 397 patients were recruited in this study, and all completed the basic data collection. Self-designed questionnaire were validated based on pre-test among 10 HIV patients. Four-time surveys were complimented by doctors in clinic at one month of follow-up, six months of follow-up, twelve months of follow-up and sixteen months of follow-up, and questionnaires were filled out by doctors. Figure 1 shows that the follow-up rates were 95.7%, 73.2%, and 77.6% for the 1-month, 6-month, and 12-month follow-up points, respectively.

Adherence Measures

In this study, adherence to ART was calculated based on three items in a questionnaire completed by subjects during the follow-up visits. The three items were “Have you ever missed a dose of the drug in the last month?”, “Have you ever taken the wrong drug in the last month?” and “Did you ever have a desire to stop taking the drug in the last month?”. Patients responding to “yes” to any of the three questions were considered “sub-optimally adherent”, whereas patients responding “no” to all three items were considered “adherent”. Patients were also asked to report the reason for and frequency of missed doses/wrong doses/cessation of ART as well as possible factors.

Other key variables

Epidemiological data, such as age, education background, marriage, alcohol use, and sexual behavior were self-reported during follow-up survey. CD4+ T cell count were obtained from patient medical files at every follow-up.

Statistical Analysis

Statistical analyses were performed using SPSS statistical software (version 19.0). Descriptive statistics included mean, median, frequency, and rate or proportion. Chi-square tests and trend chi-square tests were used to compare categorical variables. Generalized Estimating Equations models were used to explore possible associations between the dependent variable and independent variables. Crude risk ratios (CRR), adjusted risk ratios (ARR), and 95% confidence intervals (CI) were calculated to evaluate the association between ART-initial CD4 cell counts and ART adherence. A p value less than 0.05 was considered statistically significant.

Results

Table 1 shows the comparison of sociodemographic characteristics at baseline and follow-up. No statistically significant differences in the distribution of age, education background, or marriage were found between participants at baseline and the 1-month, 6-month, and 12-month follow-up points (Table 1). 82.6%, 80.9% and 79.9% were fully adherent to the treatment at 1-month, 6-months and 12-months after starting ART, respectively. There were no significant differences between the three groups for adherence rates (P>0.05). A significant difference was found in the number of missed doses, with rates of 13.7%, 16.8%, 19.2% at 1-month, 6-months, and 12-months, respectively (trend chi-square=4.692, p=0.030). The rate of taking the wrong medicine or stopping ART was lower than 5% in follow-up, as shown in Table 2. The most common reasons for missed doses were forgetting to take the drug, which accounted for 53.3%, 59.6%, 65.5% of missed doses at 1-month, 6-months, and 12-months of follow-up, respectively. The second most commonly reported reason for missing doses was forgetting to carry the tablets, which accounted for 37.8%, 29.8%, and 22.4% of missed doses at 1-month, 6-months, and 12-months, respectively. AZT was the most commonly missed medicine, accounting for 11.0%, 15.8%, 18.6% at 1-month, 6-months, and 12-months of follow-up, respectively. A Generalized Estimating Equations model was applied to explore the impact of ART-initial CD4 cell count on ART adherence, controlling for sociodemographic variables (age, education background), alcohol use, and anal sex as confounders.

Table 1: Comparison of sociodemographic characteristics between subjects at baseline and follow-up.
Table 2: The change in adherence in last month of follow-up.

| Adherence          | 1 month  | 6 months | 12 months | χ²  | P   |
|--------------------|----------|----------|-----------|-----|-----|
| Yes                | 82.6(314/380) | 80.9(237/291) | 79.9(246/308) | 0.857 | 0.651 |
| Non                | 17.4(66/380)   | 19.1(54/291)    | 20.1(62/308)   |      |     |
| Missed taking drug |          |          |           | 3.799 | 0.15 |
| Yes                | 13.7(52/380)   | 16.8(49/291)    | 19.2(50/308)   |      |     |
| No                 | 86.3(328/380)  | 83.2(242/291)   | 80.8(249/308)  |      |     |
| Took wrong drug    |          |          |           | 6.568 | 0.037 |
| Yes                | 5.0(19/380)    | 2.7(8/291)      | 1.6(5/308)     |      |     |
| No                 | 95.0(361/380)  | 97.3(283/291)   | 98.4(303/308)  |      |     |
| Stopped taking drug|          |          |           |      |     |
| Yes                | 1.1(4/380)     | 0.3(1/291)      | 0.3(1/308)     |      |     |
| No                 | 98.9(376/380)  | 99.7(290/291)   | 99.7(307/308)  |      |     |
| Reason for missing dose |   |        |           |      |     |
| Forgot             | 53.3(24/45)    | 59.6(28/47)     | 65.5(38/58)    |      |     |
| Afraid of being caught | 6.7(3/45)    | 4.3(2/47)       | 5.2(3/58)      |      |     |
| Forgot to carry    | 37.8(17/45)    | 29.8(14/47)     | 22.4(13/58)    |      |     |

Note: Missing data on reason for missing dose at 1, 6, 12 months were 21, 7, 3, respectively;

Patients with ART-initial CD4 cell counts >500 cells/mm³ were compared to those with CD4 cell counts <500 cells/mm³. There was no difference in the rate of adherence between these groups at 1-month, 6-months, or 12-months of follow-up (ARR=0.765, 95%CI=0.476,1.230). Furthermore, the study found that being over 30 years of age was protective against non-adherence to ART (ARR=0.641, 95%CI=0.441, 0.931), compared to being 30 years of age younger. Alcohol use was an independent risk factor for ART adherence. The risk of non-adherence among alcohol users was 1.809 times that of non-alcohol users in this group of HIV-positive MSM (ARR=1.809, 95%CI=1.266, 2.584) (Table 3).

Table 3: Predictors of non-adherence and the effect of early ART initiation to adherence by GEE model.

| Variable                        | Rate of non-adherence (1 month) | Rate of non-adherence (6 months) | Rate of non-adherence (12 months) | CRR (95%CI) | P    | ARR (95%CI) | P    |
|---------------------------------|---------------------------------|---------------------------------|-----------------------------------|------------|------|------------|------|
| Age                             | 17.7(44/249)                    | 21.3(43/202)                    | 23.2(47/203)                      | 1          | 1    | 0.641(0.441-0.931) | 0.019 |
|                                | 0-30                             |                                 |                                   | 0.159      | 0.272 |
|                                | 17.2(22/128)                     | 12.5(11/88)                     | 14.7(15/102)                      | 0.637(0.441-0.931) | 0.001 |
|                                | >30                              |                                 |                                   | 0.016      | 0.019 |
|                                | Education                        |                                 |                                   | 1          | 1    | 1.308(0.900-1.900) | 0.845(1.816) |
|                                | Senior high school and under     |                                 |                                   | 1.239      |      | 1.016(0.630-1.618) | 0.770 |
|                                | Greater than senior high school  |                                 |                                   | 1          | 1    | 1.016(0.630-1.618) | 0.770 |
|                                | Uses alcohol                     |                                 |                                   | 0.001      | 0.001 |
Discussion

This cohort study was conducted over nearly 2 years, and the follow-up rates were 74.6%, 81.1%, 55.8% at the 6-month, 12-month, and >12 months follow-up points, respectively. The most probable reason for the lower follow-up rate at >12 months is that this is a dynamic cohort study and some patients were only enrolled in this study for less than 1 year. No significant differences were observed for socio-demographic characteristics between five follow-up points, according to chi-square tests. The goal of this study was to describe the rate of ART adherence among HIV-positive MSM by analyzing cohort data from self-reported questionnaires. We found adherence rates to ART at 1, 6, 12, and >12 months of follow-up were decreased only slightly from 82.6% to 78.3%, with no significant differences in these rates. This adherence rate is similar to reports of rates in other Chinese cities [16-17] and is higher than that in Zambia (59.9%) [18]. This difference in adherence may be explained by different methods for measuring adherence, ART management models, and patient characteristics. Xixi hospital in Hangzhou is engaged in the ART management in Hangzhou, while the CDC was in charge of this work 4 years ago.

This change in management somehow decreased adherence to ART because the hospital did not receive enough support to conduct the work. However, there has recently been a slight change in adherence because the hospital received funding, and patients are now more likely to follow their doctor’s suggestions and management. This is likely why the adherence rates did not change over 4 follow-up points. However, previous research has suggested that adherence should be maintained at a minimum of 95% for better viral load suppression and immune system recovery [19]. Therefore, adherence rates still need to be improved in Hangzhou.

The main reason for non-adherence in this study was missed doses (>10%) followed by incorrect doses (<1%) and cessation of taking ART (<1%). The most commonly missed drugs were AZT and TDF. The most commonly reported reason for missing doses was forgetting to take the dose (almost 50%), followed by forget to carry the drugs (22.4%-37.8%). The results of this study are similar to those reported by other studies [20-21]. In China, patients need to take many tablets in different bottles every day, which increases the adherence difficulty for MSM who have formal jobs. There appears to be a common belief that reminder settings, multifunctional boxes, and case management are good for methods to remind patients to take their drugs and that these methods increase ART adherence [20,22-23].

In 2013, the WHO revised the HIV treatment guidelines to state that initiating ART at a CD4 cell count threshold of 500 cells/mm³ for HIV patients was recommended [24]. The WHO guidelines were updated in 2015 to recommend ART initiation at any CD4 cell count. China has consistently followed these guidelines, initiating ART if CD4 cell counts were less than 500 cells/mm³ in 2013 and initiating ART in all patients diagnosed as HIV-positive regardless of their CD4 cell count. In this study, approximately 15.5% of early diagnosed (CD4 cell count ≥500/cells/mm³) MSM received ART in Hangzhou, and this number will likely increase in the next few decades. The worldwide effect of early initiation of ART on adherence is unclear. The results of this study indicate that there is no relationship between ART-initial CD4 cell count and ART adherence among MSM, controlling for confounding factors such as age, education, alcohol use, and anal sex.

This is an important finding that demonstrates that patients initiating ART with high CD4 cell count will likely adhere to the regimen as well as patients with lower CD4 cell counts. This dynamic may be explained by the fact that patient perceptions on when to start ART can differ from their actions [25]. One study found that 78.4% of patients were willing to start ART when their CD4 count reached 500 cells/mm³.
CD4 counts were ≥500/cells/mm³ [25]. Additionally, in another study by our research group, we surveyed the acceptance of early ART among HIV-negative MSM in Hangzhou and found that 82.4% MSM were willing to initiate ART at any CD4 cell count (unpublished). Furthermore, a study in South Africa has revealed that viral suppression rates at 3, 6, 12 and 18 months were above 85% with no statistically significant differences for participants stating ART at different CD4 cell counts [25].

Adherence to ART is affected by many factors [14-15,26]. In this study, other important factors relating to ART non-adherence included having an education level greater than the completion of senior high school and reporting having had anal sex in the last month. MSM have a higher level of educational and a greater knowledge of HIV than other high-risk populations [27]. Educated patients may receive more information related to initiating ART and can thus weight the drawbacks and acknowledge the benefits on an individual level [28-29]. MSM who recently had anal sex are more likely not to adhere to their ART regimen, which may be due to the inconvenience of taking the medication if they are having sex with someone [14-15,26]. This study had some limitations. First, the study population only consisted of MSM, meaning that the conclusions from this study cannot be generalized to women, children, and heterosexual men. Second, patients who participated in the study may have been more health-conscious and thus may have had better adherence, which leads to selection bias. Finally, the follow-up rate of this cohort-study at >12 months was less than 70%, which might generate bias in the analysis. Future studies should investigate the relationship between ART initiation and initial CD4 cell counts in other populations to better inform ART programming.

Conclusion

In this cohort study, we have shown that ART adherence was high in Hangzhou. The main reason for non-adherence was missed doses and forgetting to take tablets was the most common reason for missing doses. There was no effect of ART-initial CD4 cell count on adherence in this study. Appropriate education and counseling by healthcare professionals might be good for patients who start ART early and may ensure successful therapy.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Ethics committee of Zhejiang Provincial Center for Disease Control and Prevention (CDC). Informed consent was signed by all subjects prior to the initiation of the study.

Authors’ Contributions

Jinlei Zheng participated in the design of the study, data management, and drafted the manuscript. Lin Chen carried out data cleaning and Mingyu Luo carried out the analysis. Miaoying Dong, Guoxiang Zheng carried out data collection. Lin He, Yun Xu, Jiang Jun, Wanjun Chen participated in data management in different research field. Xiaohong Pan, Jianhua Yu and Jiezhe Yang performed the design and coordination of the study. All authors read and approved the final manuscript.

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