Mortality Risk Factors among People Living with HIV Receiving Second-line Antiretroviral Therapy in Rural China

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Abstract

Background: Second-line antiretroviral therapy (ART) was introduced in Henan Province in 2009. Most studies of this treatment strategy focus on drug resistance and treatment failure, not on mortality. To investigate the survival and effectors of mortality among patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) who switched to second-line antiretroviral therapy (ART) in rural China. We conducted a retrospective cohort study of people living with HIV (PLHIV) who switched to second-line ART between May 1, 2010 to May 1, 2016. The data were analyzed using the Kaplan–Meier method and Cox proportional hazards models. Among 3331 PLHIV who were followed for 26988 person-years, 508 (15.3%) died and the mortality rate was 1.88/100 person-years. After adjusting for confounding factors multivariable Cox proportional hazards regression identified female (HR, 0.66; 95%CI, 0.55–0.79), age >50 years (HR, 2.69; 95%CI, 2.03–3.56), sig/window (HR, 1.26; 95%CI, 1.04–1.52) , educational status >6 years (HR, 0.78; 95%CI, 0.65–0.94), Chinese medicine(CM) (HR, 0.75; 95%CI, 0.52–0.96), liver injury (HR, 1.58; 95%CI, 1.19–2.10), CD4+ T cell count <200 cells/μl (HR, 1.94; 95%CI, 1.47-2.55), and CD4+ T cell count 200-350 cells/μl (HR, 1.37; 95%CI, 1.03–1.82) as independently variables associated with mortality. **Conclusions:** Our retrospective cohort study indicates that mortality among PLHIV who switched to second-line ART was lower compared with most other studies. However, the limitations of a retrospective cohort may have biased the data, so prospective studies should be carried out to confirm our primary results. The results of our study suggest that Chinese medicine therapy shows potential as a treatment for PLHIV.

INTRODUCTION

Acquired immune deficiency syndrome (AIDS), which induced by human immunodeficiency virus (HIV) has continued to be a worldwide public health problem and 40.1 million [33.6 million–48.6million] deaths since the start of the epidemic. Furthermore, 38.4 million [33.9 million–43.8 million] people globally were living with HIV in 2021 [1]. Thanks for the advent of ART, millions of people 's life were saved [2]. Although ART is well established effective therapy for the treatment of AIDS, but with the increase of ART duration, non-adherence, drug resistance, first-line treatment failures have become more common, and a challenge to achieving better treatment response is emerging [3]. More and more PLHIV had to be initiated second-line regimen. A study on HIV/AIDS patients' therapy in Asia reported that 19% patients had taken second-line ART [4]. Moreover, patients who switch to second-line ART after first-line treatment failure have improved outcome. However, the proportion of patients failing on second-line ART remains high. The second-line treatment failure rate was 23.1%, 19% and 12.3% after 12months treatment in resource-limited settings [5], sub-Saharan Africa [6] and Ethiopia [7] respectively. Boosted protease inhibitor (PI) + two nucleoside reverse transcriptase inhibitor (NRTI) combinations is recommended as the preferred strategy for second-line ART [8]. Recently, the World Health Organization (WHO) recommended third-line ART for PLHIV,

however, access to this therapy remains restricted by high cost and implementation barriers, so maximizing the durability of first or second-line regimens is an emerging global priority.

Henan province lies in the middle of China, being one of HIV High Incidence areas. Since 2003, ART had been used among those patients according to guidelines of the handbooks of national ART [9]. Second-line ART was implemented in Henan Province in 2009, and subsequent studies mainly focused on drug resistance and treatment failure [10, 11], little on the mortality. Hence, we design a retrospective cohort study to analysis the mortality of PLHIV after second-line ART and to identify the determinants of survival.

METHODS

Study Design, Period, and Setting

A retrospective cohort study was conducted in Henan province, which is in center of China, based on standard medical record registers. Most HIV-infected people in Henan are living in resource limited regions and were infected through paid blood supply and illegal blood plasma collecting in the 1990s and was diagnosed with HIV from 2003[12]. In 2003, China initiated a large-scale program for providing HAART free of charge. The main first-line therapy regimen comprised zidovudine (AZT)/stavudine (D4T) + didanosine (DDI) + nevirapine (NVP). However, in 2009, adult patients who experienced failure of the first-line treatment protocol have to switch to second-line ART, comprising lamivudine (3TC) + tenofovir (TDF) + lopinavir/ritonavir (Lpv/r) [13]. Henan was one of the earliest areas to begin free first-line and second-line ART as described in the National Free Antiretroviral Treatment Program (NFATP). Since 2004, the State Administration of Traditional Chinese Medicine has sponsored a national CM–AIDS Treatment Trial Program (NCMATP) for PLHIV in Henan province and this program reported elsewhere [14-16]. The information of PLHIV researched in this study were collected in the medical record registers of NFATP and NCMATP.

Study Population

All individuals in this study were in the Henan province of China where NCMATP conducted before 2009. The PLHIV were permitted to voluntarily attend NCMATP, and were given the patented Chinese drug yi ai kang (containing substances such as ginseng, huangqi, chaobaishu, Tuckahoe, Chinese angelica, chuanxiong, baishao, and Scutellariae) free of charge (five capsules three times a day) and established medical records to record their information related AIDS monthly. PLHIV in this study were switched to second-line ART between May 1, 2010 to May 1, 2016 and age ranged from 18 years to 60 years when second-line ART commenced. Individuals with incomplete data for basic demographic and clinical characteristics were excluded from the study. The study's primary endpoint was all-cause death. Individuals who were alive after 10 years of follow-up, remained alive after May 1, 2022, lost to follow-up, or discontinued ART were taken as censored data.

Data Collection and Variables

Patients' characteristics included age, sex, marital status, race, education, occupation, route of HIV infection, year(s) of confirmed HIV positive, year(s) when ART and second-line ART commenced, whether taken CM, CD4+ T cell count, anemia or not, liver injury or not, hyperlipidemia or not, year of death and year of censored were collected.

All the information from standard medical record registers of NFATP and NCMATP. The laboratory test such as the CD4+ T cell count, Hb, AST, ALT, TC and TG were the recorded value latest time from the beginning time of second-line ART in half year, if no value in half year, the variable was missing. Hyperlipidemia was defined as serum total cholesterol (TC) >6.20 mmol/L and/or serum triglyceride (TG) >2.30 mmol/L [17]. Common clinical criteria were adopted for liver injury, that is, AST/ALT[?]50 u/L, which was defined as liver injury[18]. Hemoglobin (Hb) <120g/L in adult males and Hb<110g/L in adult females, which was defined as anemia [19].

Data Analysis

Categorical variables are reported as whole numbers with proportions, and continuous variables are reported as the median and interquartile range (IQR), unless indicated otherwise. The Life-time table method was used to compute the cumulative survival rates and mortality density. Cox proportional hazard regression models were used to identify the effectors of mortality and calculate the hazard ratio (HR). Univariable Cox proportional hazard regression models were implemented first, and variables with level of significance = 0.10 were included in multivariable analysis. The results of these models were expressed as the HR and 95% confidence interval (CI). Statistical analyses were performed by using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

The variable with a level of significance = 0.05, identified using multivariable analysis, served as the explanatory variable for time-to-death after initiation of second-line ART. The Kaplan-Meier model was used to estimate the survival and log-rank test were used to compare survival curves of different groups classified according to the explanatory variable. Figures showing the survival curves were prepared using R software (version 3.6.1). Statistical analyses employed two-sided P <0.05 to indicate a significant difference.

Results

Summary of Study Population

The records of 3331 participants who initiated second-line ART from May 1, 2010 to May 1, 2016 were eligible for inclusion in this analysis. 1731(52.0%) were female and 1600 (48.0%) were male, 3321 (99.7%) were Han and 3225 (96.8%) were farmer. Among the patients in this study, a large proportion 2650 (79.6%) of the participants were infected HIV through plasma donation, 2802 (84.1%) were HIV-positive longer than 3 years and 2514 (75.5%) received ART before initiating second-line ART. The median CD4+ count was 337 (IQR:229) cells/μl. The demographic characteristics of 3331 participants receiving second-line ART are shown in Table 1.

Table 1 Demographic characteristics of 3331 PLHIV receiving second-line antiretroviral therapy

Variables	Total N=3331	Death N=508
Sex		
Female	1600 (48%)	218(42.91%)
Male	1731 (52%)	290(57.09%)
Age (year)		
<40	646 (19.4%)	65 (12.80%)
40-50	1749 (52.5%)	223 (43.90%)
50-60	936 (28.1%)	220 (43.31%)
Marital Status		
Married	2461 (73.9%)	342 (67.32%)
Sig/window	870 (26.1%)	166 (32.68%)
Educational Status		
6years	1978 (59.4%)	324 (63.78%)
>6years	1353 (40.6%)	184 (36.22%)
HIV transmission mode		
Others	681 (20.4%)	93 (18.31%)
Plasma	2650 (79.6%)	415 (81.69%)
Time on HIV Positive (year)	Time on HIV Positive (year)	
<5	529 (8.53%)	91 (17.91%)
5-8	1800 (54.0%)	287 (56.50%)
>8	1002 (30.1%)	130 (25.59%)
Time on ART before Second-line (year)	Time on ART before Second-line (year)	Time on ART before Second-line (year)
<3	817 (24.5%)	132(25.98%)
3-6	1098 (33.0%)	155 (30.51%)

>6	1416 (42.5%)	221 (43.50%)
Chinese Medicine Therapy	Chinese Medicine Therapy	
No	2684 (80.6%)	430 (84.65%)
Yes	647 (19.4%)	78 (15.35%)
CD4+ Cell Count (cells/ μl)	CD4+ Cell Count (cells/ μl)	
<200	1005 (30.2%)	202 (39.76%)
200-350	1013 (30.4%)	157 (30.91%)
350-500	691 (20.7%)	79 (15.55%)
>500	622 (18.7%)	70 (13.78%)
Anemia		
Unclear	1522(45.7%)	250(49.21%)
No	1426 (42.8%)	197 (38.78%)
Yes	383 (11.5%)	61 (12.01%)
Liver injury		
Unclear	1002 (30.1%)	163 (32.9%)
No	2043 (61.3%)	288 (56.69%)
Yes	286 (8.59%)	57 (11.22%)
Hyperlipidemia		
Unclear	2177 (65.4%)	341 (67.13%)
No	854 (25.6%)	126 (24.80%)
Yes	300 (9.01%)	41 (8.07%)

Mortality and Associated Factors

Among 3331 participants followed for (26988 person-years), 508 (15.3%) died and the mortality rate was 1.88/100 person-years. Furthermore, 96.8%, 92.7%, 88.9%, 85.5%and 81.2% of participants were alive after 2, 4, 6, 8 and 10 years, respectively, after the study commenced. The results of univariable Cox proportional hazards model analyzed factors associated with mortality of PLHIV were showed in table 2. Age 50-60 years, sig/window, CD4+ T cell count <350 cells/μL, and liver injury were risk factors of mortality. In contrast, CM therapy, female, educational status >6years decrease the risk of mortality. HIV transmission mode, time on HIV-positive, time on ART before second-line, anemia and hyperlipidemia were not the effected variable of mortality.

Thus, sex, age, CM therapy, marital status, educational status, CD4+ T cell count and liver injury were selected for multivariable Cox proportional hazards model. This analysis revealed that female (HR, 0.66; 95%CI, 0.55–0.79), age 50-60 years (HR, 2.69; 95%CI, 2.03–3.56), treated with CM therapy (HR, 0.75; 95%CI, 0.52–0.96), sig/window (HR, 1.26; 95%CI, 1.04–1.52), educational status >6years (HR, 0.78; 95%CI, 0.65–0.94), liver injury (HR, 1.58; 95%CI, 1.19–2.10), CD4+ T cell count <200 cells/μl (HR, 1.94; 95%CI, 1.47-2.55), and CD4+ T cell count 200-350 cells/μl (HR, 1.37; 95%CI, 1.03–1.82) were each independently associated with mortality.

Table 2 Mortality factors of 3331 people living with HIV(PLHIV) receiving second-line antiretroviral therapy

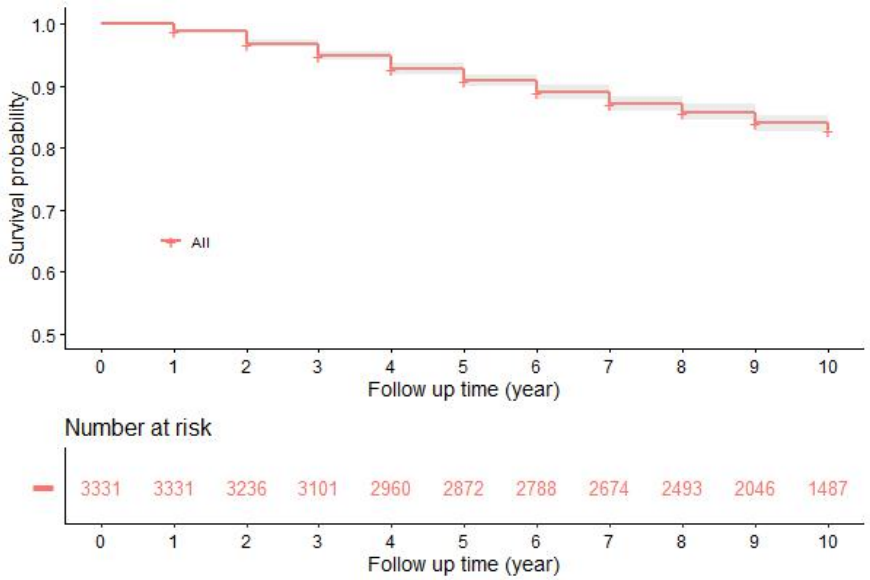
Variables	Variables	Univariable
		HR(95% CI)
Sex	Sex	
Male	Male	1[Reference]
Female	Female	0.67(0.57,0.80)
Age(year)	Age(year)	
40-	40-	1[Reference]
40-50	40-50	1.29(0.98,1.70)

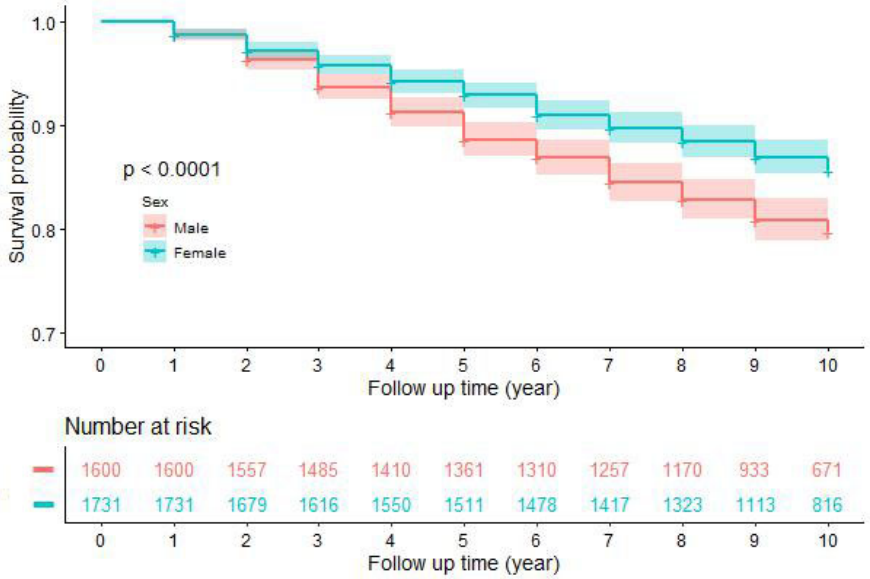
Variables	Variables	Univariable
50-60	50-60	2.56(1.94,3.38)
Marital Status	Marital Status	Marital Status
Married	Married	1[Reference]
Sig/window	Sig/window	1.41(1.18,1.70)
Educational Status	Educational Status	Educational Status
6years	[?]6years	1[Reference]
>6years	>6years	0.79(0.66,0.95)
Chinese Medicine Therapy	Chinese Medicine Therapy	Chinese Medicine Therapy
No	No	1[Reference]
Yes	Yes	0.75(0.59,0.95)
CD4+ Cell Count (cells/μl)	CD4+ Cell Count (cells/μl)	CD4+ Cell Count (cells/μl)
500+	500+	1[Reference]
350-500	350-500	1.01(0.73,1.39)
200-350	200-350	1.39(1.05,1.84)
200-	200-	1.89(1.44,2.48)
Liver Injury	Liver Injury	
No	No	1[Reference]
Yes	Yes	1.50(1.13,1.99)
Unclear	Unclear	1.25(1.03,1.51)
Factors Not Selected	Factors Not Selected	Factors Not Selected
HIV transmission mode	HIV transmission mode	HIV transmission mode
Others	Others	1[Reference]
Plasma	Plasma	1.17(0.93,1.47)
Time on HIV positive (year)	Time on HIV positive (year)	Time on HIV positive (year)
<5	<5	1[Reference]
5-8	5-8	0.93(0.74,1.18)
>8	>8	0.82(0.63,1.08)
Time on ART before Second-line (year)	Time on ART before Second-line (year)	Time on ART before Second-line (year)
<3	<3	1[Reference]
3-6	3-6	0.85(0.67,1.07)
>6	>6	0.95(0.77,1.18)
Anemia		
Yes	Yes	1[Reference]
No	No	1.04(0.79,1.37)
Unclear	Unclear	1.24(0.94,1.62)
Hyperlipidemia	Hyperlipidemia	
Yes	Yes	1[Reference]
No	No	0.84(0.63,1.12)
Unclear	Unclear	1.05(0.80,1.39)

Analysis of Risk Groups

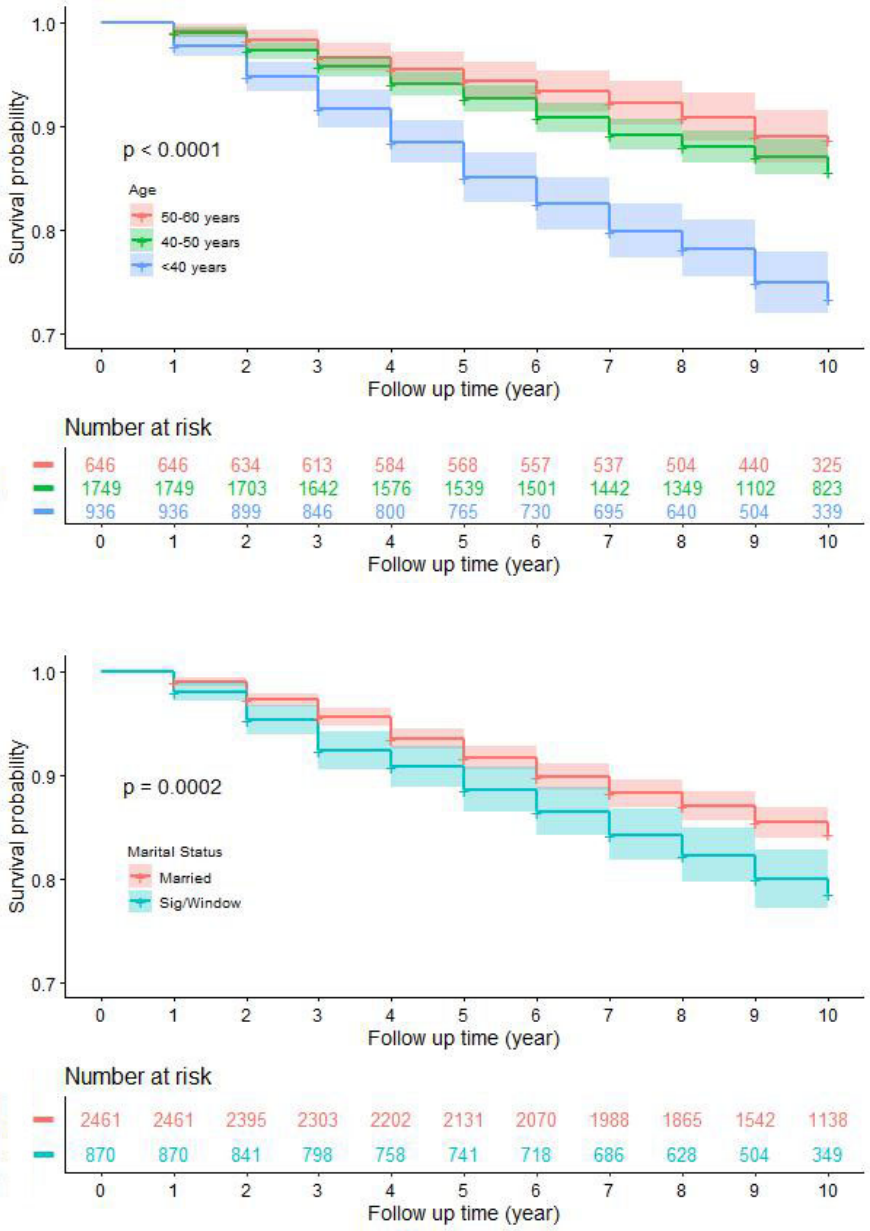
After the multivariable analysis, sex, age, marital status, educational status, CM therapy, CD4+ T cell count and liver injury were the explanatory variables on time to death after initiation of second-line ART. The survival curve of PLHIV and the cases in every year on category of explanatory variable were showed in fig1.

A B

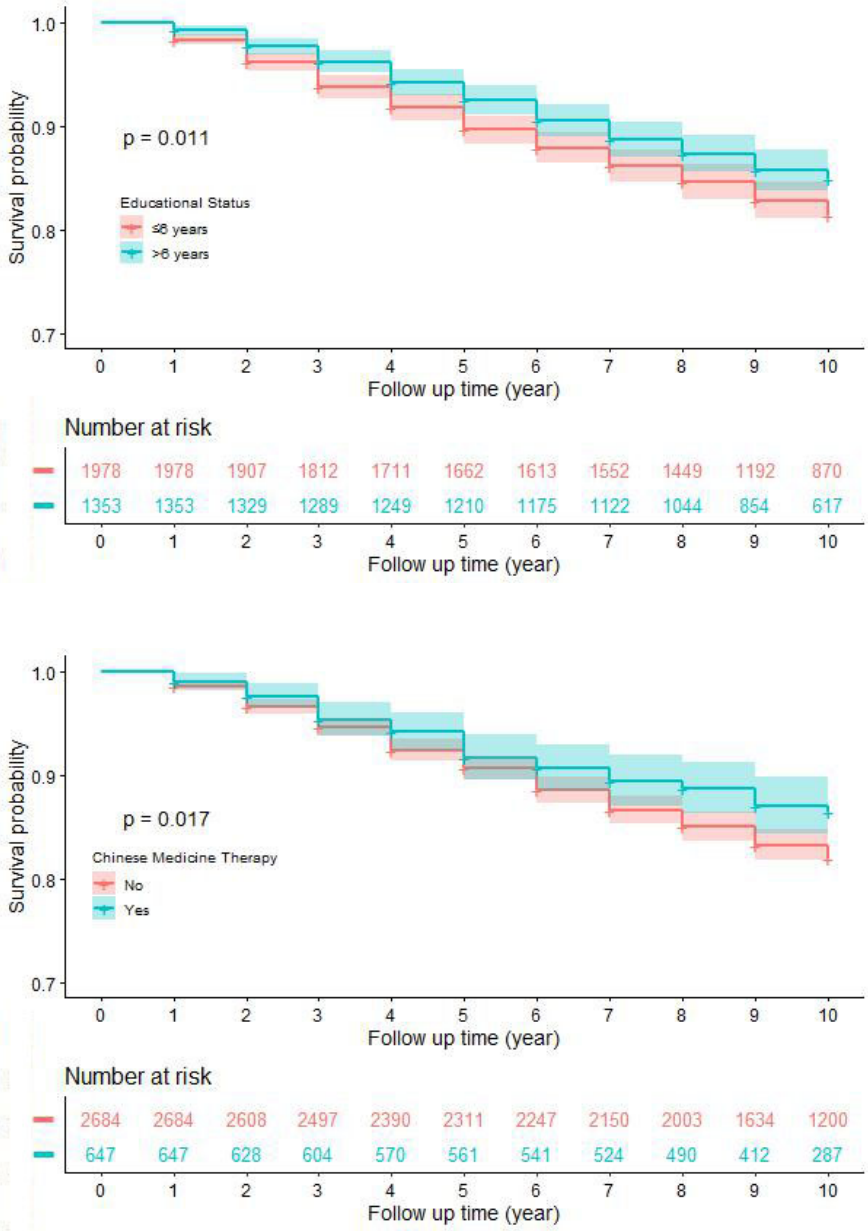




C D



E F



G H

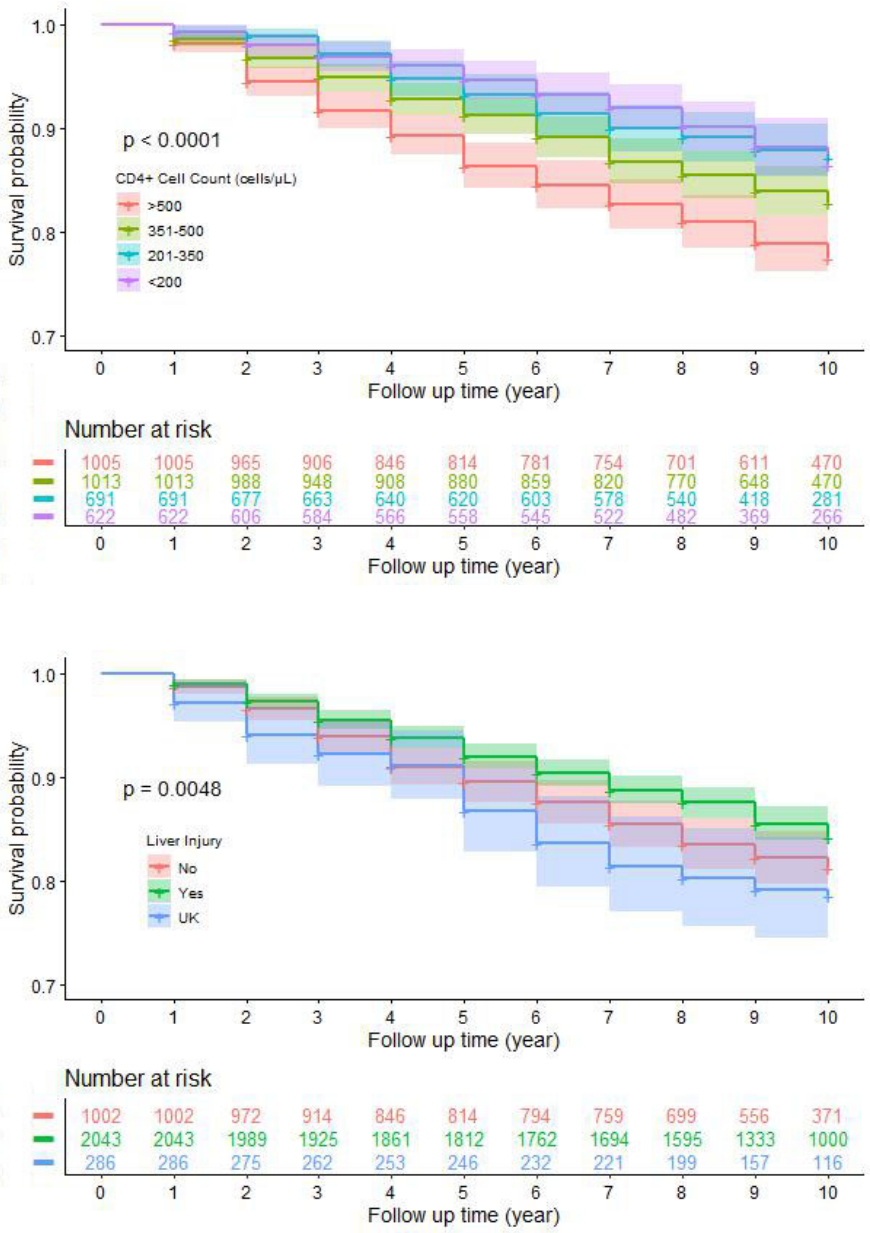


Figure 1 Kaplan-Meier survival estimator curve of PLHIV switch to second-line ART in different group. A. All, B. Sex, C. Age, D. Marital Status, E. Educational Status, F. Chinese Medicine Therapy, G. CD4+ Cell Counts, H. Liver Injury.

Discussion

The main goal of this study was to estimate the mortality rate of PLHIV after second-line ART and to identify its effectors in rural China. The overall mortality rate of was 1.88/100 person-years with a lowest level compared with the study on the survival of PLHIV after ART don' care first or second-line in Guizhou in China, where the mortality rate was with 8.53/100 person-years [20], or a study in and Henan in China, where the mortality rate was with 3.9/100 person-years [21], which it maybe the second-line ART had good efficacy. Another study conducted in African and Asian in 2010 reported the mortality rate was 4.42/100

person-years after patients switch to second-line ART [22], higher than this study. According to the global HIV statistics fact sheet reported by WHO, the mortality rate of PLHIV was decline sharply [1]. The different results among the studies might be due to difference in characteristics sample, in length of study or in the study period.

The effect of gender on survival has often been the focused, but the result had varied in the literature. Here, we find a significant difference between women and men as most studies report that women had a lower risk of death than men [23, 24]. The results of studies vary on the association of marriage with survival. Here, we find that single/window individuals are a risk factor for failure in second-line ART, which is consistent with some research findings. For example, A multivariable analysis showed that single status (unmarried or divorced) was a risk factors for PLHIV with second-line ART [25]. Older age was a higher risk of death, we report that the HR of death among PLHIV older than 50 years was 2.56 times that of those under 40, patients with 40-50 years old was not show higher HR of death compared with those under 40. Some studies have reported that older PLHIV had more comorbidities and be significantly associated with second-line ART failure [26]. Here we show that level of education was significantly associated with mortality. Compared to patients with an education level <6 years, patients with an education level >6 years have a 0.8-fold higher risk of death.

A lower CD4+ T cell count at switch to second-line was independent risk factor on time to death, which accordance with many studies. The HR of death among PLHIV with CD4+ cell count lower than 200 cells/μl was 1.89 times that of higher than 500 cells/μl. Patients with lower CD4+ cell count were found to be significantly associated with second-line ART failure and have higher probability of developing different opportunistic infections [27], all those more were apt to cause death. Anemia has been documented as a risk factor for morbidity and mortality in these patients, even if the CD4+ cell count and viral load are controlled [28-30]. However, in our study the anemia had not affect the mortality of PLHIV with second-line ART. AST/ALT[?]50 u/L, which was defined as liver injury [18], was the risk factor of death of PLHIV. In this study, we find that participants with liver injury have a 1.58-fold higher risk of death compared with these participants who without liver injury. Some study show that liver injury may induce cirrhosis and hepatocellular carcinoma and thereby increase the risk of death of PLHIV [31, 32].

Here we show that the mortality rate of PLHIV in the CM group was 1.48/100 person-years (HR, 0.75; 95%CI, 0.52–0.96) compared with 1.98/100 person-years of participants who were not treated with CM. The result suggested that CM combined with second-line ART could better increased the survival and lengthened the lifetime of PLHIV. In Henan, CM has been used to treat HIV/AIDS for decade, many effects of CM on HIV/AIDS have been shown. For example, CM reduces plasma HIV viral loads, increases CD4+ T cell counts, promotes immune reconstitution, diminishes signs and symptoms, improves health-related quality of life, and reduces the adverse effects of antiretroviral drugs [33-36].

STUDY LIMITATIONS

The data of this study extracted from the normal medical record which can veritably reflect the outcome of the current second-line ART management. As a retrospective study, selection bias was possibly introduced because of the fact that patients with incomplete records would be excluded. Some important variables associated with mortality like the viral load and body mass index when switch to second-line ART which were not recorded for most of the patients. Adherence of ART was confirmed variable don't record in the normal medical record.

CONCLUSION

We show here that mortality among PLHIV who switch to second-line ART was lower compared with most other studies. The result of our study suggest that CM based on ART was a potential treatment for PLHIV. However, the limitations of a retrospective cohort may have biased the data, so prospective studies should be carried out to confirm our primary results.

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CONFLICT OF INTEREST

There is no conflict of interest.

ETHICS STATEMENT

This study was approved by the institutional review board of the first hospital affiliated to Henan University of Traditional Chinese Medicine(2019HL-068). Individual informed consent was not achieved because this analysis used currently existing data collected during the course of routine treatment, and the data were reported in aggregate without the use of individual identifying information.

References

1 UNAIDS, "global HIV statistics fact sheet 2021," https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf, Accessed 26 Nov 2021.

2 Barik SK, Bansal AK, Mohanty PS, Tripathy SP, Hanna LE, Karunaianantham R et.al. Detection of Drug Resistance Mutations in the Reverse Transcriptase Gene of HIV-1-Infected North Indian Population Failing First-Line Antiretroviral Therapy "A Follow-Up Cohort Study". AIDS Res Hum Retroviruses. 2021;37(10):796-805.

3 Alene M, Awoke T, Yenit MK, Tsegaye AT, Yismaw L, Yeshambel R. Second-line antiretroviral therapy regimen change among adults living with HIV in Amhara region: a multi-centered retrospective follow-up study. BMC Res Notes. 2019; 12(1): 407.

4 Martinez-Vega R, De La Mata NL, Kumarasamy N, et al. Durability of antiretroviral therapy regimens and determinants for change in HIV-1-infected patients in the TREAT Asia HIV Observational Database (TAHOD-LITE). Antivir Ther. 2018; 23(2): 167-78.

5 Ajose O, Mookerjee S, Mills EJ, Boulle A, Ford N. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. AIDS. 2012; 26(8): 929-38.

6 Edessa D, Sisay M, Asefa F. Second-line HIV treatment failure in sub-Saharan Africa: A systematic review and meta-analysis. PloS one. 2019; 14(7): e0220159.

7 Zenebe Haftu A, Desta AA, Bezabih NM, et al. Incidence and factors associated with treatment failure among HIV infected adolescent and adult patients on second-line antiretroviral therapy in public hospitals of Northern Ethiopia: Multicenter retrospective study. PloS one. 2020; 15(9): e0239191.

8 World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. World Health Organization. Geneva, Switzerland; 2013.

9 Development of China "Free ART Manual" http://www.aizhi.org/UploadSoft/2005321103838886.pdf,Accessed Dec. 2021.

10 Zhang M, Shang M, Yang W, Chen J, Wang Z, Shang H. Treatment effect and drug-resistant mutations in Chinese AIDS patients switching to second-line antiretroviral therapy. PloS one. 2014; 9(10): e110259.

11 Chen J, Zhang M, Shang M, Yang W, Wang Z, Shang H. Research on the treatment effects and drug resistances of long-term second-line antiretroviral therapy among HIV-infected patients from Henan Province in China. BMC Infect Dis. 2018; 18(1): 571.

12 Dou Z, Chen RY, Wang Z, et al. HIV-infected former plasma donors in rural Central China: from infection to survival outcomes, 1985–2008. PloS one. 2010; 5(10): e13737.

13 Editor Group, Handbook of China's free ART program. 3rd ed. Beijing: Ren Min Wei Sheng Chu ban She; 2012.

14 Liu ZB, Wang X, Liu HJ, et al. Treatment of acquired immunodeficiency syndrome with Chinese medicine in China: opportunity, advancement and challenges. Chin J Integr Med. 2013; 19(8): 563-7.

15 Jin YT, Guo HJ, Wang X, et al. Traditional Chinese Medicine Could Increase the Survival of People Living with HIV in Rural Central China: A Retrospective Cohort Study, 2004-2012. Am J Chin Med. 2014; 42(6): 1333-44.

16 Jin YT, Liu ZB, Chen XM, et al. Survival of people living with HIV after treatment with traditional Chinese medicine in Henan province of China: a retrospective cohort study. J Tradit Chin Med. 2014; 34(4): 430-6.

17 Zhu JR, Gao RL, Zhao PP, Lu GP, Zhao D, Li JJ. Chinese guidelines for prevention and treatment of dyslipidemia in adults (2016 Revision)[J]. Chinese Journal of Circulation,2016,31(10):937-953.

18 Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA. 2000; 283(1): 74-80.

19 Erythrocyte diseases (anemia) Group, Hematology Branch of Chinese Medical Association. Multidisciplinary expert consensus on the diagnosis, treatment and prevention of iron deficiency and iron deficiency anemia (2022 edition) [J]. Chinese medical journal, 2022102 (41): 3246-3256.

20 Cao WJ, Yao YM, Wei W, Lin F, Lu JD, Yuan Z. Survival time and related factors on HIV/AIDS patients in Guizhou province from 1995 to 2018. Zhonghua liu xing bing xue za zhi. 2020; 41(4): 557-61.

21 Liang Y, Yang WJ, Sun DY, Li N, Wang Z. Survival analysis on Former Plasma Donors living with HIV/AIDS after initiation of antiretroviral therapy in Henan province, 2002-2017. Zhonghua liu xing bing xue za zhi. 2019; 40(6): 638-42.

22 Pujades-Rodríguez M, Balkan S, Arnould L, Brinkhof MA, Calmy A. Treatment failure and mortality factors in patients receiving second-line HIV therapy in resource-limited countries. JAMA. 2010; 304(3): 303-12.

23 Li M, Tang W, Bu K, et al. Mortality among People Living with HIV and AIDS in China: Implications for Enhancing Linkage. Sci Rep. 2016, 6: 28005.

24 Mangal TD, Meireles MV, Pascom ARP, de Almeida Coelho R, Benzaken AS, Hallett TB. Determinants of survival of people living with HIV/AIDS on antiretroviral therapy in Brazil 2006-2015. BMC Infect Dis. 2019; 19(1): 206.

25 Zhu, Keying., Xu, Qianlei., Xu, Qianlei., Ma, Yanmin., Li, Pengyu.. Suboptimal immune recovery and associated factors among people living with HIV/AIDS on second-line antiretroviral therapy in central China: A retrospective cohort study. Journal of medical virology, 2022, .

26 Ahn MY, Jiamsakul A, Khusuwan S, et al. The influence of age-associated comorbidities on responses to combination antiretroviral therapy in older people living with HIV. J Int AIDS Soc. 2019; 22(2): e25228.

27 Ross J, Jiamsakul A, Kumarasamy N, et al. Virological failure and HIV drug resistance among adults living with HIV on second-line antiretroviral therapy in the Asia-Pacific. HIV Med. 2021; 22(3): 201-211.

28 Lundgren JD, Mocroft A. Anemia and survival in human immunodeficiency virus. Clin Infect Dis. 2003; 37 Suppl 4: S297–S303.

29 Santiago-Rodriguez EJ, Mayor AM, Fernandez-Santos DM, Ruiz-Candelaria Y, Hunter-Mellado RF. Anemia in a cohort of HIV-infected Hispanics: prevalence, associated factors and impact on one-year mortality. BMC Res Notes. 2014; 7: 439.

30 Nigussie F, Alamer A, Mengistu Z, Tachbele E. Survival and Predictors of Mortality Among Adult HIV/AIDS Patients Initiating Highly Active Antiretroviral Therapy in Debre-Berhan Referral Hospital, Amhara, Ethiopia: A Retrospective Study. HIV/AIDS. 2020; 12: 757-768.

31 Puoti M, Moioli MC, Travi G, Rossotti R. The burden of liver disease in human immunodeficiency virus-infected patients. Semin Liver Dis. 2012; 32(2): 103-113.

32 Taborelli M, Suligoi B, Toffolutti F, Frova L, Grande E, Grippo F, et al. Excess liver-related mortality among people with AIDS compared to the general population: an Italian nationwide cohort study using multiple causes of death. HIV Med. 2020, 21(10): 642-9.

33 Jin YT, Wang X, Li ZB, et al. Survival of AIDS Patients Treated with Traditional Chinese Medicine in Rural Central China: A Retrospective Cohort Study, 2004–2012. Evid Based Complement Alternat Med. 2015, 2015: 282819.

34 Wang Y, Jin F, Wang Q, Suo Z. Long-Term Survival of AIDS Patients Treated with Only Traditional Chinese Medicine. Altern Complement Ther. 2017; 23(2): 60-2.

35 Li X, Li H, Li C, Xia W, Li A, Li W. Traditional Chinese Medicine Can Improve the Immune Reconstruction of HIV/AIDS Patients. AIDS Res Hum Retroviruses. 2020; 36(4): 258-9.

36 Wang DL, Ma SN, Ma YM, Guo HJ, Li PY, Yang CL et al. Effect of Traditional Chinese Medicine therapy on the trend in CD4+T-cell counts among patients with HIV/AIDS treated with antiretroviral therapy: a retrospective cohort study. Evid Based Complement Alternat Med, 2021, 5576612.