

Determinants of Survival Among HIV/AIDS Patients With The Second-Line Antiretroviral Therapy In Henan Province of China

Yantao Jin

the first affiliated hospital of Henan univeristy of traditional Chinese Medicine

Miao Zhang

Henan University of Traditioanl Chinese medicine

Yan-min Ma

Center for disease control and prevention of Henan Province

Hui-jun Guo

First affiliated hospital of Henan Unversity of traditional Chinese medicine

Peng-yu Li

First Affiliated Hospital of Henan University of traditional Chinese medicine

Chun-ling Yang

Henan University of traditional Chinese medicine

Dong-li Wang

Henan University of traditional Chinese medicine

Qianlei Xu

henan Universtity of traditional medicine

Zhibin Liu (✉ drlzbcn@163.com)

the first affiliated hospital of Henan univeristy of traditional Chinese Medicine

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Abstract

Background: To estimate the survival and effectors of mortality among HIV/AIDS patients switch to second-line highly active antiretroviral therapy (ART) in rural China.

Methods: A three years' retrospective cohort study was conducted and HIV/AIDS patients switched to the second-line ART between January 2009 to December 2014 enrollment. The data collected from medical records and analysis using Kaplan-Meier statistics and COX regression models.

Findings: A total of 2883 HIV/AIDS participants followed up for 8445 person-years, 183 (6.5%) died, 14(0.5%) lost follow-up and the mortality rate 2.17/100 person-years. After adjusting other confounding factors by multivariable COX regression, age older than 50 years (HR,3.37; 95%CI, 1.92-5.92), Traditional Chinese medicine therapy (HR,0.48; 95%CI, 0.33-0.71), CD4 cell count littler than 200 cells/ μ l (HR,2.97; 95%CI, 1.90-4.64), AST or ALT higher than 50 u/L (HR,1.55; 95%CI, 1.15-2.11) were each independently associated with mortality among HIV/AIDS patients switch to second-line ART.

Conclusions: Our retrospective cohort study indicates that mortality among HIV/AIDS patients switch to second-line ART lower than most other studies. However, the limitations of a retrospective cohort could have biased the study, so prospective studies should be carried out to confirm our primary results. The result of our study suggest that Chinese therapy was potential treatment for HIV/AIDS patients.

Background

Acquired immune deficiency syndrome (AIDS), which induced by human immunodeficiency virus (HIV) has continued to be a worldwide public health problem and 32.7 million deaths since the start of the epidemic. 38.0 million people globally were living with HIV in 2019[1]. Thanks for the advent of highly active antiretroviral therapy (HAART), millions of people's life were saved[2]. Although HAART is well established effective therapy for the treatment of AIDS, but with the increase of HAART 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 HIV/AIDS patients 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].

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 NRTI combinations is recommended as the preferred strategy for second-line ART[8]. Recently, the WHO recommended third-line ART for HIV/AIDS patients, however, access remains restricted by high cost and implementation barriers, so maximizing the durability of first or second-line regimens are emerging global priorities.

Henan province lies in the middle of china, being one of HIV High Incidence areas. From 2003 year, HAART had been used among those patients according to the handbooks of national ART. Second-line ART was introduced for Henan province in 2009, and from then on, most of studies on second-line ART was focusing on drug resistances and treatment failure[9, 10], little on the mortality. Hence, we design a retrospective cohort study to analysis the mortality of HIV/AIDS after second-line ART to explore the determinants of survival.

Methods

2.1 study design, period and setting

A three years' 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 [11]. China initiated a large-scale program for free HAART in 2003, with zidovudine (AZT)/ stavudine (D4T) + didanosine (DDI) + nevirapine (NVP) as the main first-line therapy regimen. But in 2009, adult patients with failure of the first-line treatment protocol have to switch to second-line ART, which is comprise of lamivudine (3TC) + tenofovir (TDF) + lopinavir/ritonavir (Lpv/r) [12]. Henan was one of the earliest areas to begin free first-line and second-line HAART as described in the National Free Antiretroviral Treatment Program (NFATP). In the last decade, Henan province has made significant strides in treating HIV/AIDS with Chinese medicine (CM) and this program reported elsewhere [13-15]. The information of HIV/AIDS patients researched in this study were collected in the medical record registers of NFATP and CM therapy.

2.2 Study population

All individuals in this study were in the area of taking CM therapy before year of 2009, switched to second-line ART between January 2009 to December 2014, older than 18 years and younger than 65 years when begin second-line ART. Individual who were incomplete data on basic variables were excluded from the study. The primary endpoint was all-cause death. Individuals without recorded deaths after three years following, or recorded lost follow-up or withdrawal ART were taken as censored individuals.

2.3 Data collection and variables

Information of individuals including age, gender, marital status, race, education, occupation, route of infection, year of HIV confirmed time, year of beginning ART and beginning second-line ART, whether taken Chinese medicine, CD4 cell count, hemoglobin (Hb), alanine aminotransferase (ALT), aspartate aminotransferase (AST) year of death, and year of censored were collected. All the information from standard medical record registers adopted by office of NTCMTP or Center for Disease Control and Prevention (CDC), Henan. The laboratory tests such as CD4 cell count, Hb, AST, ALT were the recorded

value latest time from the beginning time of second-line cART in half year, if no value in half year, the variable was missing.

2.4 Data analysis

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

The variable at 0.05 level of significance computed by multi-variable analysis were the explanatory variable on 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 curve of different groups classified by the explanatory variable. The figures of survival curve were performed by using R (version 3.6.1) software. All statistical analyses were performed Two-sided P-values less than 0.05 were considered to indicate statistical significance.

Results

Summary of population

2,883 records of individuals initiating second-line ART in center China during 2009-2014 were eligible for inclusion in this analysis, 1513(52.5%) were female and 1370 (47.5%) were male, the mean age was 48.0±8.2 years. 2867 (99.4%) were Han and 2791 (96.8%) were farmer. The comparison of Scio-Demographic characteristics of the patients at initiation of study is shown in Table 1.

Table 1 Scio-Demographic characteristics of AIDS patients at initiation of second-line cART			
Variables	Total N=2883	Censored N=2700	Death N=183
Gender			
Female	1513(52.5%)	1430(53.0%)	83(45.4%)
Male	1370(47.5%)	1270(47.0%)	100(54.6%)
Age (year)			
18-40	471 (16.3%)	457 (16.9%)	14 (7.7%)
40-50	1358 (47.1%)	1291 (47.8%)	67 (36.6%)
50-65	1054 (36.6%)	952 (35.3%)	102 (55.7%)
Marital Status			
Married	2405 (83.4%)	2254 (83.5%)	151 (82.5%)
Sig/window	478 (16.6%)	446 (16.5%)	32 (17.5%)
Race			
Han	2867 (99.4%)	2685 (99.4%)	182 (99.5%)
Others	16 (0.55%)	15 (0.56%)	1 (0.55%)
Occupational status			
Farmer	2791 (96.8%)	2613 (96.8%)	178 (97.3%)
Others	92 (3.19%)	87 (3.22%)	5 (2.73%)
Educational Status			
≤6years	769 (26.7%)	719 (26.6%)	50 (27.3%)
>6years	2114 (73.3%)	1981 (73.4%)	133 (72.7%)

Among the patients in this study, a large proportion (81.1%) of the participants were infected HIV through plasma donate, 2637 (91.4%) and 2276 (78.9%) were more than 3 years been HIV positive and taken cART before second-line cART initiation. The median CD4 count was 312 (IQR:288) cells/μl. The comparison of treatment-related, clinical characteristics of AIDS patients at initiation of second-line cART is shown in Table 2.

Table 2 Treatment-Related, clinical characteristics of AIDS patients at initiation of second-line cART			
Variables	Total N=2883	Censored N=2700	Death N=183
HIV transmission mode			
Others	545 (18.9%)	515 (19.1%)	30 (16.4%)
Plasma	2338 (81.1%)	2185 (80.9%)	153 (83.6%)
Time on HIV Positive (year)			
<3	246 (8.53%)	235 (8.70%)	11 (6.01%)
3-8	1532 (53.1%)	1425 (52.8%)	107 (58.5%)
>8	1105 (38.3%)	1040 (38.5%)	65 (35.5%)
Time on cART before Second-line (year)			
<3	607 (21.1%)	573 (21.2%)	34 (18.6%)
3-8	1687 (58.5%)	1565 (58.0%)	122 (66.7%)
>8	589 (20.4%)	562 (20.8%)	27 (14.8%)
Chinese Medicine Therapy			
no	2064 (71.6%)	1915 (70.9%)	149 (81.4%)
yes	819 (28.4%)	785 (29.1%)	34 (18.6%)
Calendar year of Second-line cART Initiation			
2009	70 (2.40%)	60 (2.2%)	10(5.5%)
2010	457 (15.9%)	422 (15.6%)	35 (19.1%)
2011	325 (11.3%)	298 (11.0%)	27 (14.8%)
2012	704 (24.4%)	660 (24.4%)	44 (24.0%)
2013	666 (23.1%)	637 (23.6%)	29 (15.8%)
2014	661 (22.9%)	623 (23.1%)	38 (20.9%)
CD4 Cell Count (cells/ μ l)			
200-	820 (28.4%)	732 (27.1%)	88 (48.1%)
200-350	812 (28.2%)	772 (28.6%)	40 (21.9%)
350-500	622 (21.6%)	593 (22.0%)	29 (15.8%)
500+	629 (21.8%)	603 (22.3%)	26 (14.2%)
Hemoglobin ()			

>110	2401 (83.1%)	2247 (83.2%)	154 (84.2%)
≤110	482 (16.9%)	453 (16.8%)	29 (15.8%)
AST or ALT (U/L)			
<50	1617 (56.1%)	1529 (56.6%)	88 (48.1%)
≥50	1266 (43.9%)	1171 (43.4%)	95 (51.9%)

The mortality and associated factors of those population

Of the 2883 participants followed for 3 years including 8445 person-years, 183 (6.5%) died, 14(0.5%) lost follow-up and the mortality rate 2.17/100 person-years. 98.0% of patients were alive after 1 year, 95.9% after 2 years, 93.5% after 3 years of initiated this study.

The results of univariable Cox proportional hazards model analyzed factors associated with mortality of AIDS patients were showed in table 3. older than 50 years, CD4 littler than 200 cells/ μ l, AST or ALT higher than 50 were the risk factors of mortality. Treated with Chinese medicine could decrease the risk of mortality. Gender, marital status, education status, time on HIV positive, time on cART before second-line and hemoglobin were not the effected variable of mortality.

Gender, age, Chinese medicine therapy, CD4 cell count and AST or ALT were selected for multivariable Cox proportional hazards model. Age older than 50 years (HR,3.37; 95%CI, 1.92-5.92), Chinese medicine therapy (HR,0.48; 95%CI, 0.33-0.71), CD4 littler than 200 cells/ μ l (HR,2.97; 95%CI, 1.90-4.64), AST or ALT higher than 50 (HR,1.55; 95%CI, 1.15-2.11) were each independently associated with mortality. The results showed in table 3.

Analysis the risk group

After the multivariable analysis, age, CD4 cell count, Chinese medicine therapy and unormal AST/ALT were the explanatory variables on time to death after initiation of second-line cART. The group of age<50 years followed for 3 years including 5395 person-years, 81 (5.5%) died, and the mortality rate 1.50/100 person-years. The group of age >50 years followed for 3 years including 3050 person-years, 102(10.0%) died, and the mortality rate 3.34/100 person-years (fig 1 A).The group of cd4>200 followed for 3 years including 6099 person-years, 95 (4.7%) died, and the mortality rate 1.56/100 person-years. The group of CD4 <200 years followed for 3 years including 2346 person-years, 88 (11.0%) died, and the mortality rate 3.75/100 person-years (fig 1 B).No Chinese therapy group followed for 3 years including 6024 person-years, 149 (7.4%) died, and the mortality rate 2.47/100 person-years. Chinese therapy group followed for 3 years including 2421 person-years, 34 (4.2%) died, and the mortality rate 1.40/100 person-years (fig 1 C). The group of AST or ALT <50 followed for 3 years including 4753.5 person-years, 88 (5.7%) died, and

the mortality rate 1.85/100 person-years. The group of AST or ALT >50 followed for 3 years including 3691.5 person-years, 95 (7.6%) died, and the mortality rate 2.57/100 person-years (fig 1 D).

Table 3 Cox proportional Hazards Model Showing the Association of variables					
Variables	3 years mortality(%)	Univariable		Multivariable	
		HR(95% CI)	P value	HR(95% CI)	P value
Gender					
Female	5.49	1[Reference]	NA	1[Reference]	NA
Male	7.30	1.30(0.97, 1.74)	0.079	1.25(0.93,1.68)	0.136
Age(year)					
18-40	2.97	1[Reference]	NA	1[Reference]	NA
40-50	4.93	1.67(0.94,2.97)	0.081	1.73(0.97,3.09)	0.062
50-65	9.68	3.24(1.85,5.67)	<0.001	3.37(1.92,5.92)	<0.001
Chinese Medicine Therapy					
no	7.22	1[Reference]	NA	1[Reference]	NA
yes	4.15	0.58(0.40,0.84)	0.004	0.48(0.33,0.71)	<0.001
CD4 Cell Count (cells/μl)					
500+	4.13	1[Reference]	NA	1[Reference]	NA
350-500	4.66	1.21(0.71,2.07)	0.488	1.25(0.73,2.14)	0.413
200-350	4.92	1.27(0.77,2.09)	0.357	1.35(0.81,2.22)	0.247
200-	10.73	2.84(1.82,4.43)	<0.001	2.97(1.91,4.64)	<0.001
AST or ALT (u/L)					
<50	5.44	1[Reference]	NA	1[Reference]	NA
\geq 50	7.50	1.39(1.04,1.86)	0.027	1.55(1.15,2.11)	0.005
Factors Not Selected					
Marital Status					
Sig/window	6.69	1[Reference]	NA	NA	NA
Married	6.27	0.95(0.65,1.39)	0.778	NA	NA
Educational Status					
\leq 6years	6.50	1[Reference]	NA	NA	NA
>6years	6.29	0.97(0.70,1.34)	0.854	NA	NA
Time on HIV positive (year)					

<3	4.47	1[Reference]	NA	NA	NA
3-8	6.98	1.52(0.82,2.83)	0.187	NA	NA
>8	5.88	1.28(0.68,2.43)	0.450	NA	NA
Time on cART before Second-line (year)					
<3	5.60	1[Reference]	NA	NA	NA
3-8	7.23	1.26(0.86,1.84)	0.235	NA	NA
>8	4.58	0.78(0.47,1.29)	0.334	NA	NA
Hemoglobin ()					
>110	6.41	1[Reference]	NA	NA	NA
≤110	6.02	0.96(0.65,1.43)	0.844	NA	NA

Discussion

The main goal of this study was to estimate the mortality rate of HIV/AIDS patients after second-line ART and to identify its effectors in rural China. The overall mortality rate of was 2.17/100 person-years with a lowest level compared with the study on the survival of HIV/AIDS patients after ART don' care first or second-line in Guizhou in China, where the mortality rate was with 8.53/100 person-years[16], or a study in and Henan in China, where the mortality rate was with 3.9/100 person-years[17], 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[18], higher than this study. According to the global HIV statistics fact sheet reported by WHO, the mortality rate of HIV/AIDS patients 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. Most studies report women had lower risk of death than men[19, 20], but in our study, there was no difference between women and men, even though adjust other effectors. Older age was a higher risk of death, we report that the HR of death among HIV/AIDS patients older than 50 years was 3.37 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 HIV/AIDS patients had more comorbidities and be significantly associated with second-line ART failure[21]. Married status and education status were not associated with mortality in our study.

lower CD4 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 HIV/AIDS patients with CD4 cell count lower than 200 cells/ μ l was 2.97 times that of higher than 500 cells/ μ l. 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[22], 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[23-25]. However, in our study the anemia had not affect the mortality of HIV/AIDS patients with second-line ART. AST/ALT \geq 50 u/L, which was defined as Liver injury[26], was the risk factor of death of HIV/AIDS patients. Liver injury would induce cirrhosis and hepatocellular carcinoma and increase the HR of death in HIV/AIDS patients [27, 28].

In our study, the mortality rate of HIV/AIDS patients in CM group was 1.40/100 person-years and the HR was 0.48 (95%CI, 0.33-0.71), compares with mortality of non-CM group, which mortality rate was 2.47/100 person-years. The result suggested CM combined with second-line ART could better increased the survival and lengthened the lifetime of HIV/AIDS patient. In Henan, CM treatment for AIDS for tens year, many effects of TCM on HIV/AIDS have been shown, such as reducing plasma HIV viral load, increasing CD4+ T cell counts, promoting immune reconstitution, ameliorating signs and symptoms, improving the health related quality of life, and counteracting the side effects of anti-retroviral drugs[29-32].

The data of this study extracted from the normal medical record which can veritable 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.

Conclusions

In brief, our retrospective cohort study indicates that mortality among HIV/AIDS patients switch to second-line ART lower than most other studies. The result of our study suggest that CM based on ART was a potential treatment for HIV/AIDS patients. However, the limitations of a retrospective cohort could have biased the study, so prospective studies should be carried out to confirm our primary results.

Declarations

Ethical Approval and Consent to participate

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.

Consent for publication

Not applicable.

Availability of supporting data

Data of the study can be available upon request from the author (YT-J)

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

QL-X and ZB-L conceived and designed the study, YT-J, M-Z, and YM-M performed the statistical analysis and drafted the manuscript, YT-J and HJ-G interpreted the data, PY-L, CL-Y and DL-W collected and tidy the data. All authors critically revised the paper and approved the final version.

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Authors' information

QL-X and ZB-L are the corresponding authors of this paper of this article.

References

1. UNAIDS: **global HIV statistics fact sheet**.
https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_enpdf 2020.
2. UNAIDS: **global AIDS update 2020**.
https://www.unaids.org/sites/default/files/media_asset/2020_global-aids-report_enpdf 2020.
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 research notes* 2019, **12**(1):407.
4. Martinez-Vega R, De La Mata NL, Kumarasamy N, Ly PS, Van Nguyen K, Merati TP, Pham TT, Lee MP, Choi JY, Ross JL *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).** *Antiviral therapy* 2018, **23**(2):167-178.
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):929-938.
 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, Bayray Kahsay A, Kidane KM, Zewdie Y, Woldearegay TW: **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. WHO: **Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach.** Geneva: © World Health Organization 2013.; 2013.
 9. 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.
 10. 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 infectious diseases* 2018, **18**(1):571.
 11. Dou Z, Chen RY, Wang Z, Ji G, Peng G, Qiao X, Fu J, Meng X, Bulterys M, Ma Y: **HIV-infected former plasma donors in rural Central China: from infection to survival outcomes, 1985–2008.** *PloS one* 2010, **5**(10):e13737.
 12. Zhang FJ WY, Wang J et al.: **Handbook of China's free ART program.** *Ren Min Wei Sheng Chu ban She* 2012.
 13. Liu ZB, Wang X, Liu HJ, Jin YT, Guo HJ, Jiang ZQ, Li Z, Xu LR: **Treatment of acquired immunodeficiency syndrome with Chinese medicine in China: opportunity, advancement and challenges.** *Chin J Integr Med* 2013, **19**(8):563-567.
 14. Jin Y, Guo H, Wang X, Chen X, Jiang Z, Hu G, Hou J, Jiang S, Yang X, Liu Y et al: **Traditional Chinese Medicine Could Increase the Survival of People Living with HIV in Rural Central China: A Retrospective Cohort Study, 2004-2012.** *The American journal of Chinese medicine* 2014, **42**(6):1333-1344.
 15. Jin Y, Liu Z, Chen X, Wang X, Wang D, Jiang Z, Liu Y, Wang J, Zou W, Guo H et al: **Survival of people living with HIV after treatment with traditional Chinese medicine in Henan province of China: a retrospective cohort study.** *Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese Medicine* 2014, **34**(4):430-436.

16. 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 = Zhonghua liuxingbingxue zazhi* 2020, **41**(4):557-561.
17. 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 = Zhonghua liuxingbingxue zazhi* 2019, **40**(6):638-642.
18. 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):303-312.
19. Li M, Tang W, Bu K, Mahapatra T, Zhang X, Feng Y, Chen F, Guo W, Wang L, Ding Z *et al*: **Mortality among People Living with HIV and AIDS in China: Implications for Enhancing Linkage**. *Scientific reports* 2016, **6**:28005.
20. 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 infectious diseases* 2019, **19**(1):206.
21. Ahn MY, Jiamsakul A, Khusuwan S, Khol V, Pham TT, Chaiwarith R, Avihingsanon A, Kumarasamy N, Wong WW, Kiertiburanakul 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.
22. Ross J, Jiamsakul A, Kumarasamy N, Azwa I, Merati TP, Do CD, Lee MP, Ly PS, Yunihastuti E, Nguyen KV *et al*: **Virological failure and HIV drug resistance among adults living with HIV on second-line antiretroviral therapy in the Asia-Pacific**. *HIV medicine* 2020.
23. Lundgren JD, Mocroft A: **Anemia and survival in human immunodeficiency virus**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2003, **37 Suppl 4**:S297-303.
24. Santiago-Rodríguez 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 research notes* 2014, **7**:439.
25. 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 (Auckland, NZ)* 2020, **12**:757-768.
26. 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.
27. Puoti M, Moioli MC, Travi G, Rossotti R: **The burden of liver disease in human immunodeficiency virus-infected patients**. *Seminars in liver disease* 2012, **32**(2):103-113.
28. Taborelli M, Suligoï B, Toffolutti F, Frova L, Grande E, Grippo F, Pappagallo M, Pugliese L, Regine V, Serraino D *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 medicine* 2020, **21**(10).
29. Jin Y, Wang X, Li Z, Jiang Z, Guo H, Liu Z, Xu L: **Survival of AIDS Patients Treated with Traditional Chinese Medicine in Rural Central China: A Retrospective Cohort Study, 2004–2012.** *Evidence-Based Complementary and Alternative Medicine* 2015.
 30. Wang Y, Jin F, Wang Q, Suo Z: **Long-Term Survival of AIDS Patients Treated with Only Traditional Chinese Medicine.** *Alternative & complementary therapies : a new bimonthly publication for health care practitioners* 2017, **23**(2):60-62.
 31. 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 research and human retroviruses* 2020, **36**(4):258-259.
 32. Liu ZB, Yang JP, Xu LR: **Effectiveness and safety of traditional Chinese medicine in treating acquired immune deficiency syndrome: 2004-2014.** *Infectious diseases of poverty* 2015, **4**:59.

Figures

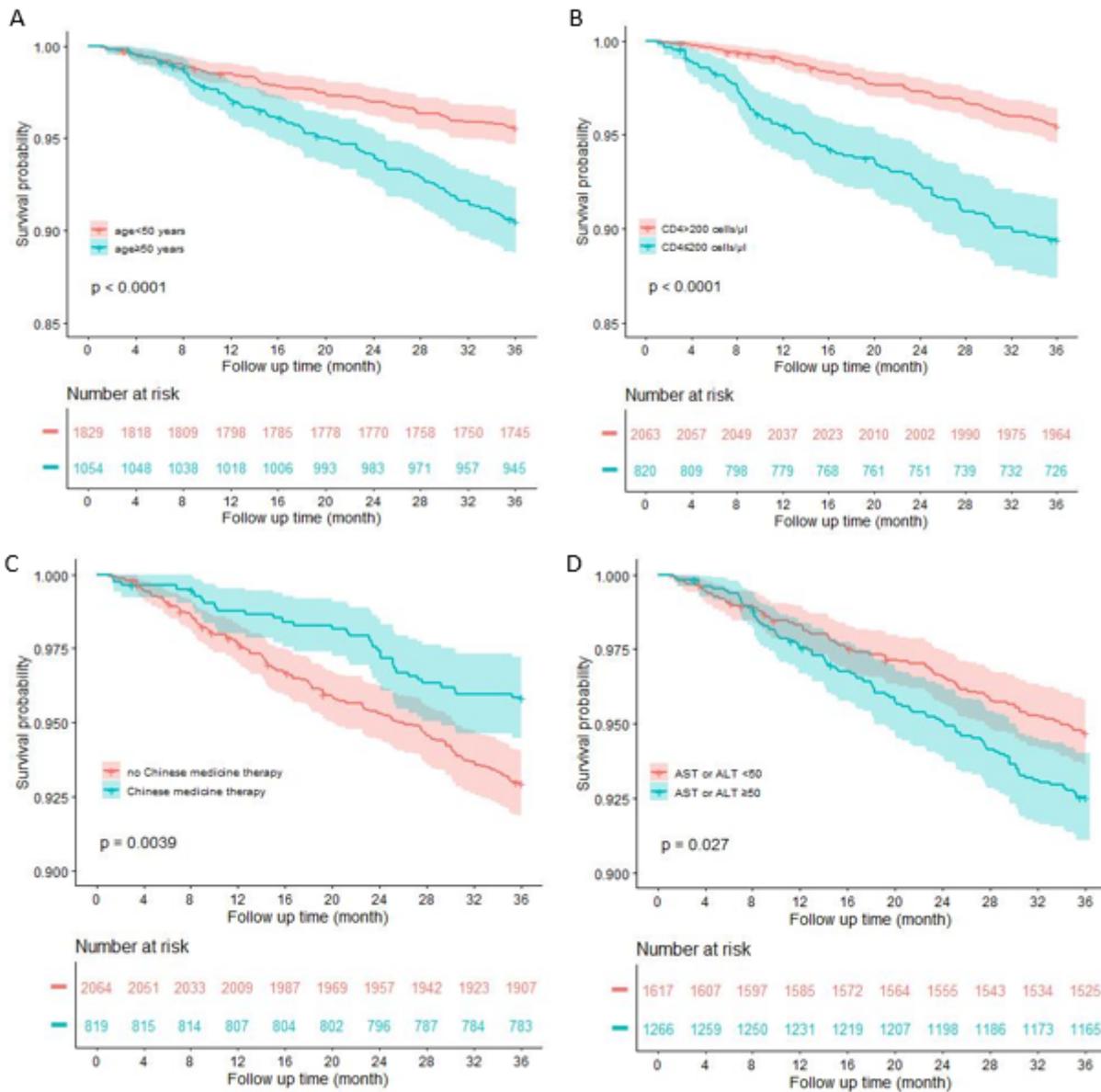


Figure 1

Kaplan-Meier survival estimator curve of HIV/AIDS patients switch to second-line ART in different group. A, between different age; B, between different CD4 cell count; C, between whether Chinese medicine therapy; D, between different AST/ALT

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