The effect of antiretroviral therapy initiation time and baseline CD4+ cell counts on AIDS-related mortality among former plasma donors in China: a 20-Year retrospective cohort study

CURRENT STATUS: UNDER REVIEW

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DOI: 10.21203/rs.2.23351/v1

SUBJECT AREAS
Infectious Diseases

KEYWORDS
HIV/AIDS, antiretroviral therapy, treatment initiation, CD4+ cell counts, AIDS-related mortality, competing risk model
Background: To estimate the influence of antiretroviral therapy (ART) initiation time on baseline CD4+ cell counts and other prognostic factors on AIDS-related death among former plasma donors patients (FPD).

Methods: A retrospective cohort study was conducted involving 11,905 HIV/AIDS patients in a high-risk area of illicit blood donation of Henan province in China between 1995 and 2016. Demographic and clinical characteristics information was collected. Hazard Ratios (HRs) for AIDS-related mortality by categories of baseline CD4+ cell counts and ART initiation time, were determined using competing risk model. Competing risk model also was used to evaluate the prognostic factors of AIDS-related mortality. The model performance was assessed by time-dependent receiver operating characteristic curve.

Results: Patients who initiated ART within 90 days of HIV/AIDS diagnosis (sHR: 0.24, 95% CI: 0.22-0.27) and baseline CD4+ cell counts of ≥500 cells/μL (sHR: 0.23, 95% CI: 0.19-0.28) were associated with lower AIDS-related mortality risk. ART initiation time >1 year and CD4+ counts >350 (sHR: 4.42, 95% CI: 3.30-5.91) had a higher AIDS-related mortality risk than ART initiation time >90 days and CD4+ counts ≤350 (sHR: 4.33, 95% CI: 3.58-5.23). Male (sHR: 1.32, 95% CI: 1.22-1.43), older age (sHR: 1.97, 95% CI: 1.59-2.46), and infection by blood transmission (sHR: 1.57, 95% CI: 1.37-1.80) were risk factors.

Conclusions: Early ART should be promoted to improve the survival of HIV/AIDS patients regardless of baseline CD4+ cell counts, especially elders, males, and infected through blood transmission.

Key words: HIV/AIDS; antiretroviral therapy; treatment initiation; CD4+ cell counts; AIDS-related mortality; competing risk model

Introduction
Human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) continues to be a major global public health issue. According to the Chinese Center for Disease Control and Prevention statistics, there are an estimated 820,756 individuals living with HIV/AIDS in China and
approximately 253,031 individuals have died from AIDS-related causes as 2018. The important reason for the widespread spread of AIDS in China is thousands of small illegal commercial plasma collection centers were established in rural areas of China between 1990 and 1994[1]. The reuse of syringes and the subsequent reinfusion of mixed red blood cells, led to most of Former Plasma Donors were infected HIV through blood transmission in China, particularly in Henan province. Up to now, Henan province is still one of the worst affected provinces in terms of HIV/AIDS[2].

Previous studies found that immediate antiretroviral therapy (ART) when CD4\(^+\) counts > 500 cells/µL could reduce mortality[3]. However, patients infected via blood transmission had higher plasma HIV load and lower CD4\(^+\) cell counts than patients infected by others transmission[4]. Besides, World Health Organization (WHO) released the second edition of the consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, recommending lifelong ART for all HIV/AIDS patients regardless of clinical status or CD4\(^+\) cell counts to reduce AIDS-related mortality[5]. Therefore, we want to know the impact of ART initiation time on AIDS-related mortality in patients with high and low CD4\(^+\) cell counts level.

HIV/AIDS patients may die of non-AIDS-related diseases. The occurrence of death of non-AIDS-related diseases prevents the occurrence of death of AIDS related diseases, and they are competitive events with each other[6, 7]. Conventional survival analysis methods consider death from non-AIDS-related causes as censored rather than the competing event, which overestimate the cumulative incidence [8] and lead to bias of the effects of covariates[9]. Competitive risk model can solve this problem, but it is rarely used in the studies of HIV/AIDS prognosis and the model performance has never been evaluated[10].

The primary aim of the present study was to explore the effect of ART initiation time, CD4\(^+\) cell counts and other prognostic factors on AIDS-related death among a cohort of FPD by competing risk model. Secondly, we also sought to evaluate the model performance of competing risk model.

**Materials & Methods**

**Study population**

Data were extracted from China’s AIDS Prevention and Control Research Cohort. All required
information of patients has been collected and uploaded to the HIV/AIDS Comprehensive Response Information Management System (CRIMS), which has been described elsewhere[11-13]. We selected a sub-cohort which is one of the most serious areas of illicit blood donation in China. The sub-cohort study was involved 13,579 HIV/AIDS patients from Zhumadian city in Henan Province between 1995 and 2016. The study included patients aged over 15 years because diagnostic criteria and severity of disease of these patients differed from those of patients below 15 years of age. Non-native patients (n = 35), patients without plasma-donation history (n = 572), patients without follow-up information (n = 264), patients without ART information (n = 729), and cases of logical error (n = 74) were excluded. The present study was limited in 11,905 HIV/AIDS patients with the eligibility criteria. This study was approved by the Ethics Committee of Henan Centre for Disease Control and Prevention.

Data Collection
HIV-infected patients and AIDS patients were followed up every three months. Demographic information (gender, age at diagnosis, educational level, marital status, and occupation) and clinical characteristics (mode of transmission, disease stage at diagnosis, CD4+ cell counts and time of ART initiation) was collected. Time from HIV diagnosis to ART initiation classified as immediate ART group (initiating within 90 days of diagnosis), delayed ART group (initiating after 90 days of diagnosis, but within 1 year), and late ART group (initiating after 1 year of diagnosis).

Definition of outcome
We defined AIDS-related death as the event of interest and non-AIDS-related death as the competing event. Causes of death were specified based on the International Classification of Diseases 10th revision (ICD-10). AIDS-related death was defined as a diagnosis of dying from AIDS-related tumors, AIDS-related opportunistic infections, AIDS-related syndrome, or other AIDS-related diseases. All the other causes of death were classified as non-AIDS-related deaths. Patients alive until May 30, 2016 or those lost during the follow-up of period were censored. Survival time was calculated from the date of HIV diagnosis to the date of death.

Statistical analysis
Cumulative incidence function (CIF) was used to estimate the probability of AIDS-related mortality, which classifies the probability of failure into that corresponding to each event[8]. Sub-distribution
proportional hazard model by Fine and Gray [14] was applied to assess the effects of covariates on the cumulative incidence function for AIDS-related deaths. Significant variables in the univariate analysis were included in the multivariate competing risk model. Proportional hazards (PH) assumption was verified based on weighted Schoenfeld residual analysis.

The model discrimination was assessed by time-dependent receiver operating characteristic curve (time-dependent ROC). The area under time-dependent receiver operating characteristic curve (AUC(t)) of more than 0.75, clearly reflects useful discrimination; 0.60 to 0.75, possibly helpful discrimination; and less than 0.60 poor discrimination[15].

All statistical analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/). The significant level was \( \alpha = 0.05 \).

**Results**

**Characteristics of HIV/AIDS patients**

In the study participants, 3,198 (26.86%) of 11,905 HIV/AIDS patients died of AIDS-related diseases, 607 (5.10%) died owing to non-AIDS-related causes, and 8,100 (68.04%) were still alive or lost to follow-up. 60.65% had already progressed to AIDS on diagnosis (Table 1).

**Cumulative Incidence**

11,905 HIV/AIDS patients were followed up for 89,070 person-years. The median follow-up time was 8.93 years and interquartile range was 3.60-11.33 years. Cumulative incidence of AIDS-related death at 1, 2, 5, 10, and 15 years after diagnosis was 9.8%, 12.9%, 19.3%, 26.0%, and 26.9%, respectively (Fig. 1).

**AIDS-related Mortality by categories of ART Initiation Time and Baseline CD4 + cell Counts**

Results of stratified by baseline CD4+ cell counts are presented in Table 2. In patients of high and low CD4+ cell counts, there were 79% and 68% decrease of AIDS-related mortality risk in immediate ART and delay ART compared with late ART. Whether among high or low CD4+ cell counts, men, elder, low educational levels and marriage are risk factors of AIDS-related mortality. Figure 3 presents AIDS-related Mortality by categories of ART Initiation Time and Baseline CD4+ cell Counts, adjusted for confounding factor. Significantly higher HRs were found with increase of ART time and decrease of
CD4^+. ART initiation time > 1 year and CD4^+ counts > 350 (sHR: 4.42, 95% CI: 3.30–5.91) had a higher AIDS-related mortality risk than ART initiation time > 90 days and CD4^+ counts ≤ 350 (sHR: 4.33, 95% CI: 3.58–5.23) (Table S1).

**Predictors of AIDS-related Mortality**

Table 2 presents the results of entire study cohort by competing risk regression model. Earlier ART provided stronger protection against death (sHR: 0.24, 95% CI: 0.22–0.27), while delayed ART provided more modest protection (sHR: 0.38, 95% CI: 0.33–0.43) relative to not receiving ART. Higher baseline CD4^+ cell counts associated with lower AIDS-related mortality. In addition, being male (sHR: 1.32, 95% CI: 1.22–1.43), older age (sHR: 1.97, 95% CI: 1.59–2.46), farmer (sHR: 1.32, 95% CI: 1.05–1.66), AIDS stage at diagnosis (sHR: 2.48, 95% CI: 2.23–2.75) and infection by blood transmission (sHR: 1.57, 95% CI: 1.37–1.80) were associated with an increased risk of AIDS-related death. High educational level and marriage were protective factors of death.

**Model performance**

As shown in the Fig. 3, AUC(t) values were above 0.73 in the 15 years, the probability of model prediction closed to the actual probability, which showed the overall model performance was good.

**Discussion**

The main results showed there were 79% and 68% decrease of AIDS-related mortality risk in immediate ART and delayed ART compared with late ART, whether in patients of high and low CD4^+ cell counts. Additional risk factors for mortality in this study were male, older age, farmer, AIDS stage at diagnosis, infection by blood transmission, low educational level, and single. Our results confirm WHO's guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. The mechanism of ART decreasing the mortality risk was primarily through viral suppression and improved immunological recovery[16]. Earlier initiation strategy of ART based on CD4^+ cell counts has been reported to prevent HIV transmission and reduce the rate of clinical events[17]. CD4^+ cell counts level is the most important laboratory indicator of immune function. When CD4^+ cell counts declines below a certain level, HIV infected individuals are at a risk of immune deficiency and more susceptible to infection, resulting in advancement of AIDS or death[18]. In present study, after
controlling for CD4$^+$ cell counts and other confounds factors, risk of AIDS-related mortality decreased with earlier of ART initiation time. We also found that patients with high baseline CD4$^+$ cell counts who initiated ART after a year had a 9% higher risk of AIDS-related death than those with lower baseline CD4$^+$ cell counts who initiated ART after 90 days but within 1 year. Patients with high CD4$^+$ levels at baseline who missed treatment opportunity would have a worse prognosis than those with lower CD4$^+$ levels at baseline[19, 20]. Arguments to delay ART initiation based on the use of a CD4$^+$ cell count threshold include concerns about drug resistance, side effects, and resource allocation[21–26]. However, previous studies have concluded that the public health benefits of immediate ART initiation more than the risks. For example, Zhao et al. discovered immediate ART when CD4$^+$ counts > 500 cells/µL could reduce the mortality within a year[27]. Our results emphasized the importance of immediate ART initiation for long-term survival among FPD with high and low CD4$^+$ cell counts. Therefore, early screening and immediate treatment after diagnosis should to be advocated, such as all patients could voluntary test, counsel, and entry into Chinese National Free Antiretroviral Treatment Program[28].

Illegal commercial plasma and blood collection activities were very common in rural central China before the national blood donation law was enacted[29]. 76.0% of HIV/AIDS patients among FPD in the present study were infected through blood transmission. Patients infected via blood transmission had higher plasma HIV load and lower CD4$^+$ cell counts than patients infected by sexual transmission, resulting in faster progression of AIDS or earlier death[30]. Mortality was higher among the older males may be attributed to late diagnosis, comorbidities, and poor immunological response to ART[31, 32]. Educational level was negatively associated with AIDS-related mortality, which is the result of the educated individuals were more likely to adopt protective measures than the others[33, 34]. Lower AIDS-related mortality risk was observed among the married, which may be explained having fewer sexual partners and being sexually safe[35].

Discrimination is an important characteristic in the evaluation of model performance[36]. In the presence of competing events, discrimination is typically characterized using the time-dependent ROC
curve[37, 38]. In this study, the AUC(t) values of each year from multivariate competing risk were above 0.80 in the first 11 years. After 12 years of follow-up, the AUC value decreased and the 95% CI expanded. The convincing reason is that the new reported mortality after 12 years was very low (AIDS-related death at 12, 13, 14, and 15 years after diagnosis was 54, 8, 2, and 0, respectively). At this time, competitive risk model is inapplicable to evaluate the prognostic factors of AIDS-related mortality.

The present study has several strengths. Firstly, our study includes large sample size and long follow-up time. Secondly, it explored association between time from HIV diagnosis to ART initiation and AIDS-related mortality among HIV/AIDS patients among high or low CD4+ cell counts levels. Finally, it was the first study to evaluate the predictors of AIDS-related mortality based on competing risk model and time-dependent ROC. Inevitably, this study has some limitations. Firstly, we don’t consider dynamic changes of CD4+ cell counts during follow-up may influence the survival in HIV/AIDS for higher proportion of missing value in CD4+ cell counts. Secondly, the compliance of ART, which may influence HIV/AIDS prognosis, was not considered in the present analysis because of unavailability of data. In future studies, details on the dynamic changes of CD4+ cell counts and ART compliance should be considered to explore their influence on AIDS-related mortality.

Conclusion
Early ART should to be promoted for improving survival of HIV/AIDS patients whether among high or low CD4+ cell counts levels, especially elders, males, and patients infected through blood transmission. Competing risk model has a good performance in the short and medium term, which provides method reference for the construction of HIV/AIDS risk prediction model in the future.

Declarations
Acknowledgments
We are grateful for the joint efforts of the members of the research group. We also extend our thanks all participants of AIDS Prevention and Control Research Cohort.

Author contributions
Conceptualization, Yongli Yang and Xuezhong Shi; Data curation, Xuening Zhang; Formal analysis,
Xuening Zhang; Funding acquisition, Xuezhong Shi; Methodology, Xuening Zhang and Weiping Zhang; Project administration, Xuezhong Shi; Software, Weiping Zhang; Supervision, Xiaocan Jia; Validation, Nian Shi and Theodore Gondwe; Writing - original draft, Xuening Zhang; Writing - review & editing, Yongli Yang, Xuening Zhang and Theodore Gondwe.

**Funding Source**

This research was funded by the National Major Science and Technology Projects of the 13th five-year plan of China (2018ZX10715009).

**Conflicts of Interest**

The authors declare no conflict of interest.

**Ethical Approval**

This study was approved by the Ethics Committee of Henan Centre for Disease Control and Prevention (2019-KY-005-02).

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found in Table S1.

**Abbreviations**

| Abbreviation | Definition |
|--------------|------------|
| ART          | antiretroviral therapy |
| AUC(t)       | the area under time-dependent receiver operating characteristic curve |
| CIF          | cumulative incidence function |
| FPD          | former plasma donors |
| HIV/AIDS     | human immunodeficiency virus and acquired immunodeficiency syndrome |
| time-dependent ROC | time-dependent receiver operating characteristic curve |

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Tables

Table 1

Characteristics of HIV/AIDS patients [n(%)]

| Variable                                      | Total       | AIDS-related mortality | Non-AIDS-related mortality | Censored |
|-----------------------------------------------|-------------|------------------------|-----------------------------|----------|
| Gender                                        | Total       | AIDS-related mortality | Non-AIDS-related mortality | Censored |
| Female                                        | 5713(47.99) | 4122(50.89)            | 1363(42.62)                 | 228(37.56) |
| Male                                          | 6192(52.01) | 3978(49.11)            | 1835(57.38)                 | 379(62.44) |
| Age at diagnosis (y)                         |             |                        |                             |          |
| 15-29                                         | 1056(8.87)  | 814(10.05)             | 212(6.63)                   | 30(4.94)  |
| 30-44                                         | 6685(56.15) | 4862(60.02)            | 1558(48.72)                 | 265(43.66) |
| 45-59                                         | 3474(29.18) | 2091(25.82)            | 1168(36.52)                 | 215(35.42) |
| ≥60                                           | 690(5.80)   | 333(4.11)              | 260(8.13)                   | 97(15.98)  |
| Educational level                             |             |                        |                             |          |
| Illiteracy                                    | 1431(12.02) | 787(9.72)              | 565(17.67)                  | 79(13.01)  |
| Primary school                                | 5537(46.51) | 3739(46.16)            | 1546(48.34)                 | 252(41.52) |
| Junior high school                            | 4501(37.81) | 3266(40.32)            | 994(31.08)                  | 241(39.77) |
| Senior high school and above                  | 436(3.66)   | 308(3.80)              | 93(2.91)                    | 35(5.77)   |
| Marital status                                |             |                        |                             |          |
| Single                                        | 747(6.27)   | 430(5.31)              | 272(8.51)                   | 45(7.41)   |
| Married                                       | 8500(71.40) | 5797(71.57)            | 2319(72.51)                 | 384(63.26) |
| Divorced or widowed                           | 2658(22.33) | 1873(23.12)            | 607(18.98)                  | 178(29.33) |
| Occupation                                    |             |                        |                             |          |
| Others                                        | 596(5.01)   | 431(5.32)              | 118(3.69)                   | 47(7.74)   |
| Farmer                                        | 11309(94.99)| 7669(94.68)            | 3080(96.31)                 | 560(92.2)  |
| Transmission                                  |             |                        |                             |          |
| Sexual                                        | 2150(18.06) | 1616(19.95)            | 380(11.88)                  | 154(25.37) |
| Blood                                         | 9575(80.43) | 6376(78.72)            | 2756(86.18)                 | 443(72.98) |
| Others                                        | 180(1.51)   | 108(1.33)              | 62(1.94)                    | 10(1.62)   |
| Disease stage at diagnosis                    |             |                        |                             |          |
| HIV                                           | 4685(39.35) | 3734(46.10)            | 754(23.58)                  | 197(32.45) |
| AIDS                                          | 7220(60.65) | 4366(53.9)             | 2444(76.42)                 | 410(67.55) |
| Time from HIV diagnosis to ART initiation     |             |                        |                             |          |
| Immediate ART (≤90d)                          | 7713(64.79) | 5633(69.54)            | 1737(54.32)                 | 343(56.51) |
| Delayed ART (>90d)                            | 2808(22.59) | 2113(26.09)            | 589(18.42)                  | 106(17.46) |
| Late ART (>1y)                                | 1384(11.63) | 354(4.37)              | 872(27.27)                  | 158(26.0)  |
| Baseline CD4⁺ cell counts [cells/μL]           |             |                        |                             |          |
| ≤200                                          | 5282(44.37) | 3169(39.12)            | 1821(56.94)                 | 292(48.1)  |
| 201-350                                       | 2876(24.16) | 2280(28.15)            | 469(14.66)                  | 127(20.92) |
| 351-500                                       | 1548(13.00) | 1277(15.77)            | 202(6.32)                   | 69(11.37)  |
| >500                                          | 1005(8.44)  | 867(10.70)             | 101(3.16)                   | 37(6.17)   |
| Untested                                      | 1194(10.03) | 507(6.26)              | 605(18.92)                  | 82(13.51)  |

Note: ART: antiretroviral therapy; HIV: human immunodeficiency virus; AIDS: acquired immune deficiency syndrome
Table 2
Prognostic factors of Entire Study Cohort and of each subgroup based on Baseline CD4+ cell counts

| Variable                                | Entire Study Cohort | Baseline CD4+ cell counts(cells/μL) |
|-----------------------------------------|---------------------|------------------------------------|
|                                         |                     | High(≤350)                         |
|                                         |                     | Low(>350)                          |
| Gender                                  |                     | 1.32(1.22-1.43)                    |
| Male                                    |                     | 1.34(1.11-1.63)                    |
| Female                                  | 1(Reference)        | 1.45(1.13-1.85)                    |
| Age at diagnosis (years)                |                     | 1.14(0.98-1.33)                    |
| 15-29                                   | 1(Reference)        | 1.56(0.97-2.52)                    |
| 30-44                                   | 1.78(1.52-2.10)     | 1.31(0.8-2.14)                     |
| ≥60                                     | 1.97(1.59-2.46)     | 3.44(2.11-5.61)                    |
| Educational level                       |                     | 6.68(3.63-12.29)                   |
| Illiteracy                              | 1(Reference)        | 9.04(4.75-17.22)                   |
| Primary school                          | 0.76(0.68-0.85)     | 1(Reference)                       |
| Junior high school                      | 0.69(0.61-0.78)     | 0.82(0.63-1.06)                    |
| Senior high school and above            | 0.68(0.53-0.88)     | 0.79(0.39-1.58)                    |
| Marital status                          | 1(Reference)        | 1(Reference)                       |
| Single                                  | 0.82(0.69-0.97)     | 0.82(0.63-1.06)                    |
| Married                                 | 0.56(0.47-0.68)     | 0.81(0.6-1.08)                     |
| Divorced or widowed                     | 1(Reference)        | 1(Reference)                       |
| Occupation                              | 1(Reference)        | 1(Reference)                       |
| Others                                  | 1.32(1.05-1.66)     | 1.56(0.76-3.23)                    |
| Farmer                                  | 1.34(0.98-1.83)     | 1.14(0.75-1.73)                    |
| Transmission                            | 1.57(1.37-1.80)     | 2.13(0.64-7.15)                    |
| Sexual                                  | 1(Reference)        | 1.17(0.22-6.3)                     |
| Blood                                   | 1.19(0.83-1.71)     | 1(Reference)                       |
| Others                                  | 2.13(0.64-7.15)     | 1.17(0.22-6.3)                     |
| Disease stage at diagnosis              |                     | 1(Reference)                       |
| HIV                                     | 1(Reference)        | 1(Reference)                       |
| AIDS                                    | 2.48(2.23-2.75)     | 2.28(1.77-2.93)                    |
| Time from HIV diagnosis to ART initiation|                     | 2.05(1.49-2.83)                    |
| Immediate ART (≤90d)                    | 0.24(0.22-0.27)     | 0.21(0.15-0.28)                    |
| Delayed ART (>90d)                      | 0.38(0.33-0.43)     | 0.32(0.22-0.45)                    |
| Late ART (>1y)                          | 1(Reference)        | 1(Reference)                       |
| Baseline CD4+ cell counts(cells/μL)     |                     | 1(Reference)                       |
| ≤200                                    | 0.43(0.39-0.48)     | 0.21(0.15-0.28)                    |
| 201-350                                 | 0.34(0.29-0.39)     | 0.32(0.22-0.45)                    |
| 351-500                                 | 0.23(0.19-0.28)     | 0.32(0.21-0.47)                    |
| >500                                    | 1.57(1.39-1.77)     | 1(Reference)                       |

Note: ART: antiretroviral therapy; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome

Figures
The median follow-up time was 8.93 years and interquartile range was 3.60-11.33 years.

Cumulative incidence of AIDS-related death at 1, 2, 5, 10, and 15 years after diagnosis was 9.8%, 12.9%, 19.3%, 26.0%, and 26.9%, respectively.

Figure 1
AUC(t) values were above 0.73 in the 15 years, the probability of model prediction closed to the actual probability, which showed the overall model performance was good.
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