Determinants of Progression to AIDS and Death Following HIV Diagnosis: A Retrospective Cohort Study in Wuhan, China

Hongbo Jiang¹, Nianhua Xie², Beibei Cao¹, Li Tan¹, Yunzhou Fan¹, Fan Zhang¹, Zhongzhao Yao², Li Liu¹*, Shaofa Nie¹*

¹Department of Epidemiology and Biostatistics, and the Ministry of Education Key Lab of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, ²Wuhan Center for Disease Control and Prevention, Wuhan, China

Abstract

Objective: To identify determinants associated with disease progression and death following human immunodeficiency virus (HIV) diagnosis.

Methods: Disease progression data from the diagnosis of HIV infection or acquiring immunodeficiency syndrome (AIDS) to February 29, 2012 were retrospectively collected from the national surveillance system databases and the national treatment database in Wuhan, China. Kaplan-Meier method, Logistic regression and Cox proportional hazards model were applied to identify the related factors of progression to AIDS or death following HIV diagnosis.

Results: By the end of February 2012, 181 of 691 HIV infectors developed to AIDS, and 129 of 470 AIDS patients died among whom 289 cases received concurrent HIV/AIDS diagnosis. Compared with men infected through homosexual behavior, injection drug users possessed sharply decreased hazard ratio (HR) for progression to AIDS following HIV diagnosis ([HR = 0.31, 95% confidence interval (CI), 0.18–0.54, P = 4.01 × 10⁻⁵]). HIV infectors at least 60 years presented 1.15-fold (HR = 2.15, 95% CI, 1.15–4.03, P = 0.017) increased risk to develop AIDS when compared with those aged 17–29 years. Similarly, AIDS patients with diagnosis ages between 50 and 59 years were at a 1.60-fold higher risk of death (HR = 2.60, 95% CI, 1.18–5.72, P = 0.017) compared to those aged 19–29 years. AIDS patients with more CD4⁺ T-cells within 6 months at diagnosis (cell/µL) presented lower risk of death (HR = 0.29 for 50- vs <50, 95% CI, 0.15–0.59, P = 0.001). The highly active antiretroviral therapy (HAART) delayed progression to AIDS from HIV diagnosis (HR = 0.15, 95% CI, 0.07–0.34, P = 6.46 × 10⁻⁶) and reduced the risk of death after AIDS diagnosis (HR = 0.02, 95% CI, 0.01–0.04, P = 7.25 × 10⁻³²).

Conclusions: Progression to AIDS and death following HIV diagnosis differed in age at diagnosis, transmission categories, CD4⁺ T-cell counts and HAART. Effective interventions should target those at higher risk for morbidity or mortality, ensuring early diagnosis and timely treatment to slow down the disease progression.

Introduction

Since China’s first acquired immunodeficiency syndrome (AIDS) case was identified in a dying tourist in 1985 [1], human immunodeficiency virus (HIV) had spread in the country and became a complex and challenging public health concern. At the end of 2011, about 780,000 patients were living with HIV (PLHIV) in China while the estimated number of new infections and death in 2011 was 48,000 and 28,000, respectively [2].

In order to provide HIV treatment and care primarily for rural and low-income urban patients who met the national treatment guidelines, the National Free Antiretroviral Treatment Program (NFATP) was initiated in October 2002 and subsequently expanded nationwide in 2003 [3]. At the end of 2011, a total of 3,142 antiretroviral therapy (ART) providers were available nationwide, located in 2,082 counties (or districts) among 31 provinces (and autonomous regions, municipalities). The total number of people ever receiving and currently receiving treatment increased from 81,739 and 65,481 in 2009 to 155,530 and 126,448 in 2011, respectively [2]. With the advent of highly active antiretroviral therapy (HAART), progression from HIV diagnosis to AIDS has been slowed down substantially, and so has the progression to death following AIDS diagnosis [4,5,6,7,8].

Despite this dramatic achievement, there remain questions about whether survival differs in specific subpopulations and what factors may drive such variation. Previous studies have suggested that age, gender, transmission category, educational level, marital status, and CD4⁺ T-cell count [4,9,10,11,12] might be markers for differences in access to treatment, adherence, or disease severity at diagnosis, ultimately leading to disparities in survival. Moreover, it
would also be meaningful work to find out factors [13] which may be associated with progression to AIDS. However, most of these observations have been made from western countries and the corresponding situation in China is far from clear. Besides, little evidence has addressed the determinants associated with AIDS progression after HIV diagnosis [9,14]. Against this background, we used data from Wuhan Center for Disease Control and Prevention (CDC) through the national surveillance system and the national treatment database to determine the related factors of progression to AIDS or death following HIV diagnosis in Wuhan, China, aiming to attain better understanding about the disease progression in developing countries.

### Methods

Subjects recruited in this study were identified through the two national databases, namely national surveillance system and national treatment database. In China, all HIV/AIDS cases diagnosed are compulsorily reported to CDC through the national surveillance system, which was upgraded to China Information System for Disease Control and Prevention (CISDCP) in 2003 [15]. The national treatment database which was established in late 2004, including data on current patients who met the national treatment criteria and those treated before 2004 [3,16,17,18]. The national treatment criteria referred to World Health Organization disease stage III or IV, CD4+ T-cell count <200 cells/µL (increasing to <350/µL in 2008), or total lymphocyte count <1200 cells/µL. HIV infectors and AIDS patients were followed.
up with a face-to-face interview every six months and three months, respectively. After each visit, local health care workers completed a standardized case report form (CRF) and faxed the form to the Chinese CDC via Datafax (Clinical DataFax Systems) [18]. These CRFs were then maintained in an ongoing observational treatment database [3]. Wuhan, the capital city of Hubei province in central China, had built the web-based reporting system of conventional infectious disease network, and realized on-line direct report infectious disease situation in September 2003, and then upgraded the system to special reporting system of AIDS and tuberculosis in 2005 [19]. Before 2003, the information of HIV/AIDS cases was recorded and then sent to Wuhan CDC via emails. After the reporting system was built, the information was inputted into the system by the staff of Wuhan CDC. Data obtained from the epidemiological database of the national surveillance system included demographic characteristics, transmission category, date of diagnosis, date of death (if applicable), and data from the national treatment database included date of treatment, drug regimens and so on.

Ethics Statement

The written consents were obtained from the Wuhan Center for Disease Control and Prevention which declared their willing to participate in the study and the data relating to disease progression of HIV/AIDS cases can be extracted from the national surveillance system databases and the national treatment database. All information was de-identified and only aggregated data were used for data analysis. The study was approved by the institutional review board of Tongji Medical College of Huazhong University of Science and Technology.

HIV Diagnosis to AIDS

We used data to determine disease progression to AIDS following HIV diagnosis among adolescents and adults (≥13 years) and selected variables at HIV diagnosis in Wuhan, China.

| Characteristics               | Persons with HIV diagnosis | P value | Adjust OR (95% CI)* | P value |
|-------------------------------|-----------------------------|---------|---------------------|---------|
| **Sex**                       |                             |         |                     |         |
| male                          | 1.00                        | 0.016   | 1.00                | 0.472   |
| female                        | 0.46 (0.30–0.72)            | 0.82 (0.49–1.30) |
| **Age(years)**                |                             |         |                     |         |
| 17–**                         | 1.00                        | 0.016   | 1.00                | 0.275   |
| 30–                           | 2.02 (1.30–3.13)            | 1.59 (0.94–2.69) |
| 40–                           | 1.75 (1.08–2.84)            | 1.11 (0.94–2.07) |
| 50–                           | 1.28 (0.70–2.37)            | 0.93 (0.43–2.00) |
| ≥60                           | 2.07 (1.01–4.06)            | 0.87 (0.38–1.98) |
| **Transmission category**     |                             |         |                     |         |
| MSM                           | 1.00                        | 3.82 × 10⁻⁷ | 0.002               |
| Blood                         | 2.63 (1.79–3.88)            | 1.01 × 10⁻⁶ | 1.81 (1.13–2.88) |
| IDU                           | 1.96 (1.11–3.46)            | 0.021   | 0.95 (0.51–1.79) |
| Unknown/other                 | 1.40 (0.28–6.91)            | 0.681   | 0.57 (0.10–3.27) |
| **Marital status**            |                             |         |                     |         |
| Single                        | 1.00                        | 1.68 × 10⁻⁴ | 0.538               |
| Married                       | 2.29 (1.51–3.46)            | 8.98 × 10⁻⁵ | 1.38 (0.78–2.45) |
| Widowed/divorced              | 1.88 (1.24–2.85)            | 0.003   | 1.24 (0.71–2.17) |
| **Education******            |                             |         |                     |         |
| Primary                       | 1.00                        | 2.26 × 10⁻⁵ | 0.970               |
| Secondary                     | 0.80 (0.46–1.40)            | 0.435   | 1.00                |
| College/university            | 0.31 (0.16–0.59)            | 3.97 × 10⁻⁴ | 0.52 (0.32–0.85) |
| Unknown/other                 | 3.11 (0.68–14.23)           | 0.144   | 2.48 (0.47–12.98) |
| **HAART**                     |                             |         |                     |         |
| No                            | 1.00                        | 5.19 × 10⁻⁷ | 2.61 × 10⁻⁴        |
| Yes                           | 0.12 (0.05–0.27)            | 0.13 (0.05–0.30) |

Data reported to Centers for Disease Control and Prevention from 1994 to February 29, 2012.

*Adjusted for factors statistically significant in univariate analysis.

**The youngest person who met the inclusion criteria was 17 years old.

****Primary: illiterate or primary school, Secondary: middle school, high school or technical secondary school.

MSM = men who had sex with men; IDU = injection drug user; HC = heterosexual contact with a high-risk individual or person with HIV infection or AIDS; Blood = blood transfusion or blood products; AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; OR = odds ratio; CI = confidence interval.

doi:10.1371/journal.pone.0083078.t002
We included subjects who (1) were Wuhan residents and had been reported by Wuhan CDC, (2) were confirmed to be HIV-infected by a positive Western blot result, and (3) were aged older than 13 years at diagnosis. Given difference in disease progression between adolescents and adults, we excluded infectors who were infected perinatally or younger than 13 years of age at diagnosis [20]. Cases were followed up from the date of HIV diagnosis until February 29, 2012 (i.e., censoring date). It was assumed that the disease did not progress to AIDS for subjects who were free of AIDS diagnosis report at censoring date. Persons who died during the follow-up period were censored at date of death. Of 695 HIV infectors met the inclusion criteria above, 4 (0.58%) were excluded from the analyses because of too much missing information.

AIDS Diagnosis to Death

We also determined survival among adolescents and adults (≥13 years old) diagnosed with AIDS. Subjects who met the inclusion criteria in the part of HIV diagnosis to AIDS, and received a diagnosis of AIDS either by an AIDS-defining illness or by having a CD4+ T-cell count <200 cells/μL before February 29, 2012 were included. Patients were followed up from the date of AIDS diagnosis until February 29, 2012. Individuals free of death at censoring date were assumed to be alive. Patients who died not due to AIDS or AIDS-defining illnesses during the follow-up period were censored at date of death. Of 472 AIDS cases met the criteria above, 2 (0.42%) were excluded from the analyses because of too much missing information.

Table 3. HRs and 95% CIs of progressing to AIDS among HIV infectors, Cox proportional hazard model results according to demographic factors and selected variables at HIV diagnosis, Wuhan, China.

| Characteristics         | Persons with HIV diagnosis | P value | Adjust HR (95% CI)* | P value |
|-------------------------|----------------------------|---------|---------------------|---------|
| Sex                     |                            |         |                     |         |
| male                    | 1.00                       | 0.200   | 1.00                | 0.560   |
| female                  | 0.79 (0.55–1.13)           | 0.005   | 0.89 (0.59–1.33)    | 0.163   |
| Age (years)             |                            |         |                     |         |
| 17–**                   | 1.00                       |         |                     |         |
| 30–                     | 1.30 (0.89–1.90)           | 0.178   | 1.47 (0.96–2.26)    | 0.079   |
| 40–                     | 1.33 (0.88–2.02)           | 0.180   | 1.35 (0.83–2.20)    | 0.228   |
| 50–                     | 1.53 (0.89–2.63)           | 0.123   | 1.59 (0.85–2.96)    | 0.145   |
| ≥60                     | 2.97 (1.69–5.21)           | 0.005   | 2.15 (1.15–4.03)    | 0.017   |
| x² for trend            | 3.93                       |         |                     | 0.048   |
| Transmission category   |                            |         |                     |         |
| MSM                     | 1.00                       | 0.001   | 1.00                | 0.188   |
| HC                      | 1.28 (0.91–1.81)           | 0.162   | 0.88 (0.59–1.30)    | 0.508   |
| Blood                   | 2.24 (1.26–3.99)           | 0.006   | 1.60 (0.86–2.96)    | 0.137   |
| IDU                     | 0.51 (0.30–0.85)           | 0.010   | 0.31 (0.18–0.54)    | 4.01 x 10⁻⁵ |
| Unknown/other           | 0.63 (0.15–2.60)           | 0.525   | 0.39 (0.09–1.71)    | 0.213   |
| Marital status          |                            |         |                     |         |
| Single                  | 1.00                       | 0.094   | 0.97 (0.62–1.51)    | 0.886   |
| Married                 | 1.91 (1.35–2.76)           | 2.91 x 10⁻⁴ | 1.35 (0.86–2.12)    | 0.192   |
| Widowed/divorced        | 1.36 (0.95–1.95)           |         |                     |         |
| Education ***           |                            | 0.124   | 0.379               |         |
| Primary                 | 1.00                       | 0.094   | 0.97 (0.62–1.51)    | 0.886   |
| Secondary               | 0.85 (0.54–1.35)           | 0.495   | 0.97 (0.60–1.56)    | 0.901   |
| College/university      | 0.56 (0.32–0.99)           | 0.044   | 0.66 (0.36–1.21)    | 0.181   |
| Unknown/other           | 1.20 (0.45–3.18)           | 0.710   | 0.97 (0.35–2.64)    | 0.951   |
| x² for trend ****       | 18.88                      | <0.001  |                     |         |
| HAART                   |                            | 2.28 x 10⁻⁵ | 6.46 x 10⁻⁶       |         |
| No                      | 1.00                       | 0.017   | 0.15 (0.07–0.34)    |         |
| Yes                     |                            | 0.08–0.39 |                     |         |

Data reported to Centers for Disease Control and Prevention from 1994 to February 29, 2012.

*Relative risk adjusted for sex and the other factors statistically significant in univariate analysis.

**The youngest person who met the inclusion criteria was 17 years old.

***Primary: illiterate or primary school; Secondary: middle school, high school or technical secondary school.

****Unknown exclude.

MSM = men who had sex with men; IDU = injection drug user; HC = heterosexual contact with a high-risk individual or person with HIV infection or AIDS; Blood = blood transfusion or blood products; AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; HR = hazard ratio; CI = confidence interval.

doi:10.1371/journal.pone.0083078.t003
Data Analysis

The primary end point of the AIDS-related mortality was death attributable to AIDS or AIDS-defining illnesses. By using the overall period 1999–2002 as a whole owing to the small numbers of annual AIDS-related death during these years, then yearly from 2003 to 2011, the AIDS-related mortality was defined as the total number of subjects who died of AIDS or AIDS-defining illnesses within the specified time period divided by the sum of person-years for individuals who received a diagnosis of AIDS during the same period. The year that a person was lost to follow-up or died of AIDS was used to determine the interval for survival calculations.

Table 4. Relative survival of persons with a diagnosis of AIDS in Wuhan, China.

| Characteristics | Number Entering Interval | Percent surviving 1 year after AIDS diagnosis | Number Entering Interval | Percent surviving 3 year after AIDS diagnosis |
|-----------------|--------------------------|-----------------------------------------------|--------------------------|-----------------------------------------------|
|                 |                          | %                                             |                          | %                                             |
|                 |                          | 95% CI                                        |                          | 95% CI                                        |
| **Sex**         |                          |                                               |                          |                                               |
| Female          | 116                      | 83.49                                        | 49                       | 74.36                                         |
|                 |                          | 74.76–89.41                                  |                          | 63.93–82.49                                  |
| Male            | 354                      | 82.91                                        | 111                      | 79.90                                         |
|                 |                          | 77.96–86.85                                  |                          | 74.14–84.51                                  |
| **Age (years)** |                          |                                               |                          |                                               |
| 19–*            | 101                      | 85.13                                        | 34                       | 76.75                                         |
|                 |                          | 76.11–90.95                                  |                          | 63.16–85.87                                  |
| 30–             | 146                      | 91.37                                        | 65                       | 87.42                                         |
|                 |                          | 84.88–95.16                                  |                          | 79.26–92.52                                  |
| 40–             | 108                      | 78.20                                        | 32                       | 74.35                                         |
|                 |                          | 68.36–85.31                                  |                          | 63.30–82.52                                  |
| 50–             | 79                       | 70.49                                        | 24                       | 66.78                                         |
|                 |                          | 57.01–80.45                                  |                          | 51.82–78.04                                  |
| ≥60             | 36                       | 88.86                                        | 5                        | 79.97                                         |
|                 |                          | 69.27–96.27                                  |                          | 51.04–92.84                                  |
| **Transmission category** |              |                                               |                          |                                               |
| MSM             | 120                      | 95.23                                        | 23                       | 95.23                                         |
|                 |                          | 87.43–98.23                                  |                          | 87.43–98.23                                  |
| HC              | 245                      | 80.85                                        | 86                       | 75.34                                         |
|                 |                          | 74.75–85.62                                  |                          | 67.95–81.26                                  |
| Blood           | 57                       | 71.60                                        | 30                       | 67.37                                         |
|                 |                          | 57.37–81.80                                  |                          | 52.79–78.33                                  |
| IDU             | 39                       | 86.50                                        | 18                       | 77.13                                         |
|                 |                          | 67.66–94.76                                  |                          | 55.26–89.25                                  |
| Unknown/other   | 9                        | 1.91                                         | 3                        |                                               |
| **Marital status** |                        |                                               |                          |                                               |
| Single          | 135                      | 90.00                                        | 43                       | 85.64                                         |
|                 |                          | 82.87–94.26                                  |                          | 75.45–91.83                                  |
| Married         | 202                      | 78.00                                        | 74                       | 73.05                                         |
|                 |                          | 70.84–83.60                                  |                          | 64.94–79.58                                  |
| Widowed/divorced| 133                      | 83.69                                        | 43                       | 78.11                                         |
|                 |                          | 75.20–89.47                                  |                          | 67.33–85.70                                  |
| **Education**   |                          |                                               |                          |                                               |
| ≤Primary        | 66                       | 74.52                                        | 28                       | 67.82                                         |
|                 |                          | 61.23–83.83                                  |                          | 53.51–78.58                                  |
| Secondary       | 312                      | 83.17                                        | 101                      | 79.23                                         |
|                 |                          | 77.89–87.30                                  |                          | 72.93–84.23                                  |
| ≥College/university | 83                  | 93.09                                        | 26                       | 93.09                                         |
|                 |                          | 83.85–97.13                                  |                          | 83.85–97.13                                  |
| Unknown/other   | 9                        | 1.91                                         | 5                        |                                               |
| **CD4** T–cell count (cell/μL)** |            |                                               |                          |                                               |
| <50             | 110                      | 70.53                                        | 37                       | 63.25                                         |
|                 |                          | 61.13–79.38                                  |                          | 51.04–73.20                                  |
| 50–             | 178                      | 91.94                                        | 56                       | 89.01                                         |
|                 |                          | 84.46–95.42                                  |                          | 81.24–93.68                                  |
| ≥200            | 60                       | 97.75                                        | 21                       | 100.00                                        |
|                 |                          | –                                             |                          | –                                             |
| Unknown         | 122                      | 71.38                                        | 46                       |                                               |
| **AIDS at HIV infection diagnose** |            |                                               |                          |                                               |
| No              | 181                      | 89.51                                        | 61                       | 87.72                                         |
|                 |                          | 85.32–94.93                                  |                          | 79.18–92.91                                  |
| Yes             | 289                      | 70.97                                        | 99                       | 72.03                                         |
|                 |                          | 71.89–82.54                                  |                          | 65.21–77.73                                  |
| **HAART**       |                          |                                               |                          |                                               |
| No              | 146                      | 34.96                                        | 13                       | 21.50                                         |
|                 |                          | 24.16–45.61                                  |                          | 12.23–32.49                                  |
| Yes             | 324                      | 97.39                                        | 147                      | 95.28                                         |
|                 |                          | 94.91–98.83                                  |                          | 90.96–97.57                                  |
| **Total**       |                          |                                               |                          |                                               |
|                 | 470                      | 83.15                                        | 160                      | 78.16                                         |
|                 |                          | 79.02–86.54                                  |                          | 73.06–82.41                                  |

Data reported to Centers for Disease Control and Prevention from 1999 to February 29, 2012.

*The youngest person who met the inclusion criteria was 19 years old.

**Primary: elementary or primary school; Secondary: middle school, high school or technical secondary school.

MSM = men who had sex with men; IDU = injection drug user; HC = heterosexual contact with a high-risk individual or person with HIV infection or AIDS; Blood = blood transfusion or blood products; AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; CD4+ T–cell count = CD4+ T–cell count within 6 months at diagnosis (cell/μL); CI = confidence interval.

doi:10.1371/journal.pone.0083078.t004
other causes (e.g., other disease, suicide, accident et al) was counted as one-half of a person-year. A similar method was conducted to calculate each individual’s person-years receiving HAART during each time period. The Log-linear model was used to determine whether a decreasing trend for mortality existed. Kaplan-Meier method was used in STATA software (Stata Corp., College Station, TX) to calculate the proportions of HIV infectors who progressed to AIDS and relative survival proportions for AIDS patients. Stratified analyses were conducted by sex, age at AIDS diagnosis or HIV diagnosis, transmission category, marital status, educational level, receiving HAART or not, CD4+ T-cell count at AIDS diagnosis (first record within 6 months at diagnosis), and concurrent diagnosis of HIV diagnosis and AIDS or not (only for AIDS cases). The cross-table was applied to assess the linear trend in morbidity and mortality among strata of selected variables.

We used non-conditional Logistic regression analysis and Cox proportional hazard model to address potential risk factors of AIDS morbidity and mortality [21]. Univariate and multivariate non-conditional Logistic regression analyses were conducted to explore the potential factors associated with the likelihood of AIDS events or death events. Univariate Cox models were applied to assess the unadjusted relationship between morbidity or mortality and specified covariates of interest. Multivariate Cox regression analysis was conducted after adjustment for sex and factors statistically significant in univariate analysis. Data were analyzed using SPSS, version 12.0 (SPSS, Inc., USA). All hypothesis testing was based on 2-sided tests with $\alpha = 0.05$.

Results

HIV Diagnosis to AIDS

As reported to the Wuhan CDC, 691 persons received HIV diagnosis from 1994 to February 2012, of whom 181 HIV infectors developed to AIDS, 11 (1.59%) HIV infectors were lost to follow up, 456 (65.99%) HIV infectors did not progress to AIDS and were still alive, while 43 (6.22%) cases died before they progressed to AIDS. The majority of HIV infectors were male (85.14%) and attained secondary education (60.20%). 679 (98.26%) HIV infectors were Han Chinese, and the other 12 were minorities. The median age at HIV diagnosis was 34 years old, ranging from 17 to 85 years old [interquartile range (IQR): 26–46 years old]. Men who had sex with men (MSMs) accounted for 48.63%, followed by heterosexual contact (HC) with someone at high risk or with a diagnosis of HIV infection or AIDS, injection drug users (IDUs), infection through Blood (blood transfusion or blood products), and other unknown reasons (Table 1). The single persons accounted for 48.48%, and only 17.66% of HIV infectors received HAART.

The mean follow-up time of HIV infectors was 18.58±20.16 months. 17.90%, 28.15% and 57.27% of HIV infectors progressed to AIDS after one year, two years, and five years, respectively. The rate of progression to AIDS within one or three years following HIV diagnosis was similar between males and females, and it was lower for individuals receiving HAART than those did not. The proportion of HIV infectors with progression to AIDS presented no difference in age at diagnosis, transmission categories, marital statuses, educational level within one year following diagnosis. Otherwise, different proportion of HIV infectors with progression...
to AIDS arose among the groups mentioned above except educational level at three years (Table 1).

Results of univariate and multivariate non-conditional Logistic regression analyses are presented in Table 2. In the univariate analyses, sex, age at diagnosis, transmission categories, marital status, educational level and HAART were statistically significant associated with AIDS events \( (P < 0.05 \) for all). After mutual adjustment by these factors, sex, age at diagnosis, and marital status were no longer statistically significant associated with AIDS events \( (P > 0.05 \) for all). Otherwise, HIV infectors transmitted by HCs and Blood were more likely to develop AIDS compared to MSMs \( [\text{Odds ratio (OR)} = 1.81 \text{ for HCs vs MSMs}, 95\% \text{ CI}, 1.13–]

### Table 5. ORs and 95% CIs of likelihood to die of AIDS or AIDS-defining illnesses among AIDS patients, non-conditional Logistic regression analysis model results according to demographic factors and selected variables at AIDS diagnosis, Wuhan, China.

| Characteristics                          | Persons with AIDS diagnosis* | \( P \) value | Adjust OR (95% CI)** | \( P \) value |
|------------------------------------------|------------------------------|--------------|----------------------|--------------|
| **Sex**                                  |                              |              |                      |              |
| male                                     | 1.00                         | 0.212        | 1.00                 | 0.615        |
| female                                   | 0.73 (0.45–1.19)             | 0.438        | 1.26 (0.51–3.07)     |              |
| **Age (years)**                          |                              |              |                      |              |
| 19–**                                    | 1.00                         | 0.022        | 1.00                 | 0.414        |
| 30–**                                    | 0.77 (0.39–1.50)             | 0.438        | 1.51 (0.31–7.65)     | 0.596        |
| 40–**                                    | 1.30 (0.67–2.54)             | 0.443        | 2.14 (0.25–3.70)     | 0.964        |
| 50–**                                    | 2.24 (1.13–4.43)             | 0.202        | 2.14 (0.57–8.06)     | 0.260        |
| \( \geq 60 \)                            | 1.44 (0.58–3.55)             | 0.431        | 2.25 (0.58–8.82)     | 0.244        |
| **Transmission category**                |                              |              |                      |              |
| MSM                                      | 1.00                         | 3.55 \times 10^{-5} | 0.543              |              |
| HCs                                      | 7.79 (3.04–19.96)            | 1.88 \times 10^{-5} | 0.96 (0.10–8.84)     | 0.972        |
| Blood                                    | 13.42 (4.72–38.14)           | 1.11 \times 10^{-6} | 1.76 (0.26–11.97)    | 0.562        |
| IDU                                      | 7.93 (2.52–25.00)            | 4.08 \times 10^{-4} | 3.16 (0.38–26.24)    | 0.286        |
| Unknown/other                            | 18.40 (3.75–90.29)           | 3.33 \times 10^{-4} | 1.05 (0.13–8.53)     | 0.966        |
| **Marital status**                       |                              |              |                      |              |
| Single                                   | 1.00                         |              |                      |              |
| Married                                  | 3.07 (1.68–5.61)             | 2.72 \times 10^{-4} | 1.27 (0.36–4.51)     | 0.708        |
| Widowed/divorced                         | 1.89 (0.97–3.71)             | 0.062        | 1.11 (0.48–2.59)     | 0.806        |
| **Education****                          |                              |              |                      |              |
| \( \leq \text{Primary} \)                | 1.00                         | 2.93 \times 10^{-5} | 0.010              |              |
| Secondary                                | 0.52 (0.29–0.92)             | 0.026        | 0.04 (0.003–0.47)    | 0.011        |
| \( \leq \text{College/university} \)    | 0.12 (0.04–0.34)             | 6.01 \times 10^{-5} | 0.02 (0.002–0.26)    | 0.002        |
| Unknown/other                            | 3.74 (0.86–16.35)            | 0.080        | 0.01 (0.001–0.15)    | 0.001        |
| **CD4\(^+\) T-cell count (cell/\mu L)** |                              |              |                      |              |
| \(< 50 \)                                | 1.00                         | 2.60 \times 10^{-11} | 0.001              |              |
| 50–**                                    | 0.21 (0.11–0.42)             | 6.33 \times 10^{-6} | 0.30 (0.11–0.80)     | 0.017        |
| \( \geq 200 \)                           | 0.04 (0.01–0.30)             | 0.002        | 0.07 (0.01–0.68)     | 0.022        |
| Unknown                                  | 1.79 (1.04–3.08)             | 0.035        | 1.51 (0.63–3.66)     | 0.358        |
| **AIDS at HIV infection diagnosis**      |                              |              |                      |              |
| No                                       | 1.00                         |              |                      |              |
| Yes                                      | 3.17 (2.14–6.43)             | 1.91 (0.82–4.46)|              |              |
| **HAART**                                |                              |              |                      |              |
| No                                       | 1.00                         |              |                      |              |
| Yes                                      | 5.29 \times 10^{-28}         | 1.90 \times 10^{-19} |              |              |

Data reported to Centers for Disease Control and Prevention from 1999 to February 29, 2012.  
*HIV infection diagnosed with or without a concurrent diagnosis of AIDS.  
**Adjusted for sex and the other factors statistically significant in univariate analysis.  
***The youngest person who met the inclusion criteria was 19 years old.  
****Primary: illiterate or primary school, Secondary: middle school, high school or technical secondary school.  
MSM = men who had sex with men; IDU = injection drug user; HC = heterosexual contact with a high-risk individual or person with HIV infection or AIDS Blood = blood transfusion or blood products; AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; CD4\(^+\) T-cell count = CD4\(^+\) T-cell count within 6 months at diagnosis (cell/\mu L); OR = odds ratio; CI = confidence interval.  
doi:10.1371/journal.pone.0083078.t005
Table 6. HRs and 95% CIs of death among AIDS patients, Cox proportional hazard model results according to demographic factors and selected variables at AIDS diagnosis, Wuhan, China.

| Characteristics                  | Persons with AIDS diagnosis* | P value | Adjust HR (95% CI)** | P value |
|----------------------------------|-----------------------------|---------|----------------------|---------|
| **Sex**                          |                             |         |                      |         |
| Male                             | 1.00                        | 0.458   | 1.00                 | 0.963   |
| Female                           | 1.18 (0.77–1.80)            | 0.005   | 0.99 (0.59–1.66)     | 0.152   |
| **Age (years)**                  |                             |         |                      |         |
| 19–***                          | 1.00                        | 0.005   | 1.00                 |        |
| 30–                             | 0.76 (0.41–1.40)            | 0.377   | 1.41 (0.67–2.95)     | 0.362   |
| 40–                             | 1.25 (0.69–2.27)            | 0.469   | 1.61 (0.74–3.47)     | 0.227   |
| 50–                             | 2.09 (1.16–3.77)            | 0.014   | 2.60 (1.18–5.72)     | 0.017   |
| <=60                            | 1.85 (0.83–4.10)            | 0.130   | 2.17 (0.80–5.89)     | 0.128   |
| / for trend                      | 6.55                        | 0.010   |                      |         |
| **Transmission category**        |                             |         |                      |         |
| MSM                             | 1.00                        | 0.002   | 1.00                 | 0.588   |
| HC                              | 6.16 (2.47–15.34)           | 9.35 x 10^-5 | 1.23 (0.44–3.43) | 0.687   |
| Blood                           | 7.94 (2.98–21.15)           | 3.42 x 10^-5 | 0.95 (0.30–2.99) | 0.932   |
| IDU                             | 5.69 (1.94–16.67)           | 0.002   | 0.44 (0.13–1.49)     | 0.185   |
| Unknown/other                   | 14.45 (3.88–53.88)          | 6.97 x 10^-5 | 1.18 (0.27–5.18) | 0.825   |
| **Marital status**              |                             |         |                      |         |
| Single                          | 1.00                        | 0.002   | 1.00                 | 0.588   |
| Married                         | 2.63 (1.51–4.56)            | 0.001   | 0.67 (0.31–1.43)     | 0.302   |
| Widowed/divorced                | 1.79 (0.96–3.32)            | 0.066   | 0.71 (0.31–1.64)     | 0.426   |
| **Education**                   |                             |         |                      |         |
| Primary                         | 1.00                        | 2.21 x 10^-4 | 1.00                 | 0.275   |
| Secondary                       | 0.65 (0.40–1.04)            | 0.072   | 1.24 (0.73–2.09)     | 0.427   |
| College/university              | 0.17 (0.06–0.44)            | 2.28 x 10^-4 | 0.80 (0.27–2.37) | 0.685   |
| Unknown/other                   | 1.89 (0.77–4.65)            | 0.164   | 2.46 (0.88–6.87)     | 0.087   |
| / for trend                      | 18.93                       | <0.001  |                      |         |
| **CD4 T-cell count (cell/µL)**  |                             |         |                      |         |
| <=50                            | 1.00                        | 2.14 x 10^-10 | 0.05 (0.01–0.49)    | 5.01 x 10^-6  |
| 50–                              | 0.26 (0.14–0.49)            | 1.87 x 10^-5 | 0.29 (0.15–0.59)   | 0.001   |
| >=200                           | 0.05 (0.01–0.38)            | 0.004   | 0.14 (0.02–1.12)     | 0.064   |
| Unknown                         | 1.64 (1.06–2.54)            | 0.026   | 1.51 (1.00–2.69)     | 0.051   |
| / for trend                      | 31.54                       | <0.001  |                      |         |
| **AIDS at HIV infection diagnosis** |                           |         |                      |         |
| No                              | 1.00                        | 1.00    |                      |         |
| Yes                             | 3.11 (1.87–5.18)            | 0.99 (0.55–1.78) | 0.981   |
| **HAART**                       |                             |         |                      |         |
| No                              | 1.00                        | 2.42 x 10^-30 | 7.25 x 10^-25    | 0.010   |
| Yes                             | 0.02 (0.01–0.04)            | 0.02 (0.01–0.04) | 0.010   |

Data reported to Centers for Disease Control and Prevention from 1999 to February 29, 2012.

*HIV infection diagnosed with or without a concurrent diagnosis of AIDS.

**Relative risk adjusted for sex and the other factors statistically significant in univariate analysis.

***The youngest person who met the inclusion criteria was 19 years old.

****Primary: illiterate or primary school; Secondary: middle school, high school or technical secondary school.

*****Unknown exclude.

MSM = men who had sex with men; IDU = injection drug user; HC = heterosexual contact with a high-risk individual or person with HIV infection or AIDS Blood = blood transfusion or blood products; AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; CD4+ T-cell count = CD4+ T-cell count within 6 months at diagnosis (cell/µL); HR = hazard ratio; CI = confidence interval.

doi:10.1371/journal.pone.0083078.t006

2.89, P = 0.013; OR = 4.76 for Blood vs MSMs, 95% CI, 1.89–12.01, P = 0.001]. The more educated HIV infectors and those under HAART were less likely to develop AIDS (OR = 0.52 for College/university vs Secondary, 95% CI, 0.32–0.85, P = 0.010;
Table 3 shows the results of the univariate and multivariate Cox regression analysis of factors associated with the risk of progressing to AIDS. The univariate analysis demonstrated that factors, including age at diagnosis, transmission categories, marital status, educational level and HAART, had significant influence on AIDS progression. Age might be a risk factor for developing AIDS ($P_{\text{for trend}}=0.048$), whereas education turned out to be a protective factor ($P_{\text{for trend}}<0.001$). The results of the multivariate analysis after adjustment for sex and factors statistically significant in univariate analysis showed that IDUs were less likely to develop AIDS following HIV diagnosis ($HR=0.31; 95\% CI, 0.18–0.54$, $P=4.01\times10^{-6}$) compared with MSMs. The individuals aged ≥60 years had a 1.15-fold higher risk of progressing to AIDS ($HR=2.15, 95\% CI, 1.15–4.03, P=0.017$) compared with those aged 17–29 years. The HAART reduced substantially the risk of progression to AIDS ($HR=0.15, 95\% CI, 0.07–0.34, P=6.46\times10^{-16}$).

AIDS Diagnosis to Death

470 persons received AIDS diagnosis from 1999 to February 2012, of whom 129 died, including 27 censored patients who died not due to AIDS or AIDS defining diseases. 5 (1.06%) AIDS patients were lost to follow up, and 336 (71.49%) AIDS patients survived. 289 of 470 (61.46%) AIDS patients received concurrent HIV/AIDS diagnosis. The majority of AIDS patients were male (75.32%) and attained secondary education (66.38%). 454 (96.06%) AIDS patients were Han Chinese and the other 16 were minorities. The median age at AIDS diagnosis was 39 years old, ranging from 19 to 79 years old [IQR: 31–49 years old]. The married patients accounted for 42.98%, and over half (52.12%) of AIDS patients were infected through HC (Table 4). AIDS Patients with low CD4+ T-cell counts (<50 cells/μL) accounted for 23.4%, and 68.94% of patients received HAART.

The AIDS-related mortality over time among AIDS patients are shown in Figure 1. The NFATP began in 2003 in Wuhan, and thereafter increased its capacity. Compared with the AIDS-related mortality of 66.67/100 person-years in 2003, the data decreased statistically significantly each year from 2005 onward ($P<0.05$).

With regard to CD4+ T-cell count within 6 months at diagnosis, AIDS patients with more number of CD4+ T-cells within 6 months at diagnosis had lower risk of death ($HR=0.29$ for 50- vs $<50, 95\% CI, 0.15–0.59, P=0.001$). The HAART reduced the risk of death to $0.02, 95\% CI, 0.01–0.04, P=7.25\times10^{-25}$.

Discussion

Quantification of the survival after AIDS and identification of characteristics present at HIV or AIDS diagnosis offered valuable information for the better understanding about the progression of HIV infection. Our study addressed such issues and found that transmission categories and age at diagnosis were related to progression to AIDS after HIV diagnosis. Besides, Survival after AIDS diagnosis differed among age at AIDS diagnosis and number of CD4+ T-cells within 6 months at diagnosis (cell/μL). HAART reduced the risk of progression to AIDS after HIV diagnosis and death after AIDS diagnosis.

From the surveillance data, 74.86% of the Wuhan native AIDS patients survived 5 years after AIDS diagnosis. The one-year survival, two-year-survival and five-year-survival were higher than that in a study conducted in Italy (83.15% vs 80.6%, 81.03% vs 75.2% and 74.86% vs 66.4%) [22]. The different economic and health care conditions between China and Italy might probably contribute to the different survival. The AIDS-related mortality decreased statistically significantly each year from 2005 onward ($P<0.05$), compared with that in 2003, which was mostly attributable to the NFATP [9]. The reduction in mortality achieved by the NFATP was consistent with results seen in other regions and countries [23,24,25,26,27,28].

The findings of the multivariate Cox proportional hazards regression analysis revealed the potential disparities in disease
progression among persons with an HIV or AIDS diagnosis. We found that excess mortality risk exist in AIDS patients with more severe disease (lower CD4+ T-cell count at AIDS diagnosis). Consistently with previous evidence, disease severity was proved as an independent risk factor for poor survival [4,29,30], whereas, HAART acted as an independent preventive factor for delaying progression to AIDS and prolonging survival for its role in improving clinical symptoms of AIDS patients, reducing HIV RNA concentration, and maintaining immune function [4,5,6,31].

In the first edition (2005) of the China Free ART Manual, the CD4+ T-cell count criterion for treating adult patients was <200 cells/μL, and increased to <350 cells/μL in the revised (2008) version [16,17]. As a result, more people might receive HAART. Unfortunately, 61.46% of the HIV infectors in our study received a concurrent diagnosis of AIDS which was defined by a CD4+ T-cell count<200 cells/μL or by an AIDS-defining illness. 32.87% AIDS patients had very low CD4+ T-cell counts at AIDS diagnosis (<50 cells/μL). HIV diagnosis at advanced disease may indicate rapid disease progression or late diagnosis in the disease process (testing may be motivated by symptoms). Because of social or economic factors, HIV infectors might be concurrently diagnosed with AIDS at low CD4+ T-cell counts for lack of adequate care to monitor the infection and institute treatment [13]. Other factors related to receipt of treatment such as health insurance, type of insurance or competing subsistence needs [32,33], might also partly explain the differences in survival.

Older patients presented increased risk for disease progression in our analyses, which might be caused by diminished immune function and recovery and higher comorbidity [34,35,36,37,38]. An elevated risk of death associated with older age at diagnosis (HR = 1.49; 95% CI, 1.34–1.66 per 10-year increase) was found in the UK population in 2008 [8], which may provide some evidence for our results. Evidence from several studies [39,40] showed that for a given CD4+ T-cell count or viral load, older patients had a greater risk for progressing to AIDS than younger ones. However, adherence to treatment appeared to be higher among older compared with younger HIV infectors [41]. Moreover, elderly cases had increased significantly in recent years and thus more attention should be paid to these populations [42].

Decreased educational level was associated elsewhere with increased mortality [43,44]. Inadequate care for knowledge about HIV/AIDS among the lower educational level groups may delay an AIDS diagnosis until symptoms appeared [45]. Reports of disparities in HIV survival related to sex have been mixed, with some studies reporting higher survival among female individuals [36,46], some reporting it among male individuals [47], or no difference [38,48,49]. Consistent with a previous study [50], IDUs presented less likely to progress to AIDS following HIV diagnosis compared with MSMs, which might be related to the younger age of IDUs compared with that of MSMs. The results of univariate Cox regression analyses showed that patients transmitted by Blood culture among districts in China. HIV diagnosis, which was unsure whether the results could be extrapolated nationally due to the diversity of economy and culture among districts in China.

Conclusions

In summary, progression to AIDS and death following HIV diagnosis differed in age at diagnosis, transmission categories and CD4+ T-cell counts. HAART had significantly delayed the progression to AIDS following HIV diagnosis and improved the survival of AIDS patients. Thus effective interventions should target those at higher risk for morbidity or mortality, ensuring early diagnosis and timely treatment to slow down the disease progression. In future, a prospective study with larger size of sample should be carried out to obtain more information about the AIDS progression.

Acknowledgments

We acknowledge the staff of the Wuhan Centers for Disease Control, who spent many hours working with us in obtaining, verifying, and cleaning the data used in this study.

Author Contributions

Conceived and designed the experiments: HJ ZY LL SN. Analyzed the data: HJ NX BC. Wrote the paper: HJ NX BC LT YF FZ ZY LL SN. Data gathering: ZY SN.

References

1. Settle E. (2003) AIDS in China: An annotated chronology 1985–2003. Montreal: China AIDS Survey. Available: http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressrepor t/2012countries/ce_CN_Narrative_Report[1].pdf. Accessed 2013 Jun 13.
2. Zhang FJ, Pan J, Yu L, Wou Y, Zhao Y (2005) Current progress of China’s free ART program. Cell Res 15: 877–882.
3. Pezzotti P, Dorrucci M, Donisi A, Cusini M, Mazzarello G, et al. (2003) [Survival, progression to AIDS and immunosuppression in HIV-positive

Determinants of Progression of HIV/AIDS Cases

4. Egger M, May M, Chene G, Phillips AN, Ledergerber B, et al. (2002) Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 360: 119–129.
5. Wong KH, Chan KCW, Lee SS (2004) Delayed progression to death and to AIDS in a Hong Kong cohort of patients with advanced HIV type 1 disease during the era of highly active antiretroviral therapy. Clinical infectious diseases 39: 853–860.
6. Pezzotti P, Dorrucci M, Donisi A, Cusini M, Mazzarello G, et al. (2003) [Survival, progression to AIDS and immunosuppression in HIV-positive
individuals before and after the introduction of the highly active antiretroviral therapy (HAART). Epidemiol Prev 27: 348–355.

7. Holgrave DR (2005) Causes of the decline in AIDS deaths, United States, 1995–2002: prevention, treatment or both? Int J STD AIDS 16: 777–781.

8. Ewing FM, Bhakoo L, McLean K, Hawkins D, Fisher M, et al. (2008) Survival following HIV infection of a cohort followed up from seroconversion in the UK. AIDS 22: 89–95.

9. Zhang F, Dou Z, Yu L, Xu J, Jiao JH, et al. (2008) The effect of highly active antiretroviral therapy on mortality among HIV-infected former plasma donors in China. Clin Infect Dis 47: 825–833.

10. Malta M, Bastos FI, da Silva CM, Pereira GF, Lucena FF, et al. (2009) Survival following HIV infection of a cohort followed up from seroconversion in the UK. AIDS 22: 89–95.

11. Monge S, Jarrín I, Pérez-Hoyos S, Ferreros I, García-Olalla P, et al. (2011) Differential survival benefit of universal HAART access in Brazil: a nation-wide comparison of outcomes of using drugs versus men who have sex with men. J Acquir Immune Defic Syndr 52: 629–635.

12. Lewden C, Bouteloup V, De Wit S, Sabin C, Microfi A, et al. (2012) All-cause mortality in treated HIV-infected adults with CD4+/CD8+ 500/mm3 compared with the general population: evidence from a large European observational cohort collaboration. Int J Epidemiol 41: 443–455.

13. Monge S, Jarrín I, Pérez-Hoyos S, Ferreros I, García-Olalla P, et al. (2011) Differential survival benefit of universal HAART access in Brazil: a nation-wide comparison of outcomes of using drugs versus men who have sex with men. J Acquir Immune Defic Syndr 52: 629–635.

14. Mongs S, Jarrín I, Pérez-Hoyos S, Ferreros I, García-Olalla P, et al. (2011) Differential survival benefit of universal HAART access in Brazil: a nation-wide comparison of outcomes of using drugs versus men who have sex with men. J Acquir Immune Defic Syndr 52: 629–635.

15. Wang L, Wang Y, Jin S, Wu Z, Chin DP, et al. (2008) Emergence and control of highly active antiretroviral therapy (HAART). Epidemiol Prev 27: 348–355.