“Late for testing, early for antiretroviral therapy, less likely to die”: results from a large HIV cohort study in China, 2006–2014

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Abstract

Background: Timely HIV testing and initiation of antiretroviral therapy are two major determinants of survival for HIV-infected individuals. Our study aimed to explore the trend of late HIV/AIDS diagnoses and to assess the factors associated with these late diagnoses in China between 2006 and 2014.

Methods: We used data from the Chinese Comprehensive Response Information Management System of HIV/AIDS (CRIMS). All individuals who tested positive for HIV between 2006 and 2014 in China and were at least 15 years of age were included. A late diagnosis was defined as an instance in which an individual was diagnosed as having AIDS or WHO stage 3 or 4 HIV/AIDS, or had a CD4 cell count less than 200 cells/mm³ at the time of diagnosis.

Results: Among the 528,234 individuals (≥15 years old) newly diagnosed with HIV between 2006 and 2014, 179,700 (34.0%) people were considered to have received late diagnoses. The late diagnosis rate decreased from 33.9% in 2006 to 29.7% in 2014 (P<0.01). Late diagnoses were more likely to be found among those who were 45–54 years old (adjusted odds ratio [aOR]: 3.25, 95% confidence interval [CI]: 3.17–3.34) or 55+ years old (OR: 2.94, 95% CI: 2.86–3.02), male (aOR: 1.15, 95% CI: 1.13,1.17), employed as a farmer or rural laborer (aOR: 1.13, 95% CI: 1.11–1.14), infected through blood or plasma transfusion (aOR: 4.18, 95% CI: 4.02, 4.35), diagnosed at hospitals (OR: 1.17, 95% CI: 1.15, 1.19), of Han ethnicity (aOR: 1.30, 95% CI: 1.28, 1.32), and married (OR: 1.12, 95% CI: 1.11,1.13). Of those people living with HIV (PLHIV) who received late diagnoses, 7.4%(8637) and 46.1%(28,462) ultimately died with or without receiving antiretroviral therapy within a year of diagnosis, respectively.

Conclusion: A large proportion of individuals with HIV/AIDS receive late diagnoses, and this proportion has witnessed a slight decline in recent years. Expanded testing is needed to increase early HIV diagnosis and antiretroviral therapy should be recommended to all diagnosed individuals as early as possible to reduce AIDS-related death.

Keywords: Late diagnosis, Early mortality, ART, China

Background

The introduction and expansion of highly active antiretroviral therapy (HAART) has proven to be one of the most remarkable public health measures in reducing the morbidity and mortality caused by the Human Immunodeficiency Virus (HIV) [1–4]. UNAIDS sets an ambitious treatment target to help end the AIDS epidemic: By 2020, 90% of all people living with HIV know their HIV status, 90% of people with diagnosed HIV receive antiretroviral therapy (ART) and 90% of all people on HIV treatment achieve viral suppression [5]. However, delayed testing as well as stigma and discrimination against infected individuals places them at risk of receiving delayed antiretroviral therapy [6].

Early detection of HIV infection is a critical factor in controlling the spread of HIV [7]. Timely ART is associated with a better prognosis among HIV-infected individuals and lower rates of disease progression [8]. Prompt linkages with health care systems at the start of ART yields the maximum benefits of HIV medical treatment for people living with HIV (PLHIV) [9] while decreasing the sexual transmission rate of HIV [10–13].
late diagnosis is detrimental to both the individual infected with HIV and the community for two reasons. First, in the absence of timely initiation of ART, the majority of patients will suffer the deleterious effects of HIV infection due to the gradual failure of the immune system, ranging from infection by opportunistic diseases to even death. Second, the propensity for HIV transmission by untested and hence unaware PLHIV is greater [14, 15] than for those made aware of their HIV status.

Developed countries such as the USA, Canada, and the European Union have been successful in addressing some of the key operational factors hindering the effective management of diseases affecting PLHIV [16–21]. However, it is estimated that 30% of PLHIV in the European Union [9] remain undiagnosed, while evidence from the United States suggests that 25% of the undiagnosed population is responsible for the transmission of new HIV infections in 54% of cases [7, 22].

The proportion of those who received late diagnoses in industrialized countries is most often reported in between 25 and 45% of all newly HIV-diagnosed cases [23]. Though the largest proportion of undiagnosed PLHIV resides in developing countries, little research describing their characteristics has been conducted in these settings. In China, HIV voluntary counseling and testing (VCT) is free and can be widely accessed in urban areas. However, this free testing strategy has not been able to prevent a large proportion of cases of late HIV diagnosis for several reasons [24]. Incomplete HIV screening among STD patients in China has been cited as one important cause of missed opportunities for HIV testing [25].

Our study aimed to identify characteristics and trends of cases of late HIV/AIDS diagnosis, and to assess the factors associated with late diagnosis, early mortality, and ART initiation in China between 2006 and 2014.

Methods
Data sources and definitions
In China, all newly diagnosed HIV/AIDS cases and all recipients of free ART are registered into the Chinese Comprehensive Response Information Management System of HIV/AIDS (CRIMS). CRIMS is managed by the National Centre for AIDS/STD Control and Prevention (NCAIDS) of the Chinese Centre for Disease Control and Prevention (China CDC) and includes the National Case Reporting Database (NCRD) and the National Free Antiretroviral Therapy Database (NFATD). The NCRD collects data on newly diagnosed HIV/AIDS cases, including demographic characteristics, route of infection, site of HIV diagnosis or blood sample source, date of diagnosis, laboratory test results with corresponding test date, and date of death. These cases are followed up every 6 months. During each follow-up, CD4 cell count, counseling and behavior intervention, and other referral services are performed. The NCRD also collects additional data during each follow-up visit, including changes in demographic information, disease stage, CD4 cell count, information on behavioral determinants, and details of ART. The NFATD includes all cases that meet the national treatment criteria and have received free treatment. In China, the national criteria for treatment is a CD4 cell count of less than 350 cells/mm$^3$ (as of 2009) and later, of less than 500 cells/mm$^3$ (as of 2014), or being reported as having AIDS, or having WHO stage 3 or 4 HIV/AIDS and having been referred for ART [26–29]. Information on the individual’s drug regimen during each follow-up visit is recorded and then uploaded to the CRIMS.

A detailed description of the NCRD and NFATD has been published elsewhere [26], including a discussion of quality control of lab work [28]. There have been several important ART studies based on the data from these two systems in recent years [27–29]. In this study, we updated the results in continuation with earlier findings from the cohort study [27]. We included all newly diagnosed HIV/AIDS cases between 1 January 2006 and 31 December 2014 in mainland China involving individuals aged 15 years and over and excluded individuals who could not be located by local CDCs during follow-up visits.

There were several explanations for the term “late diagnosis” [30–32]. In this study, we classified a case as a "late diagnosis" if an individual was reported as 1) having been diagnosed with AIDS or 2) having been diagnosed with WHO stage 3 or 4 HIV/AIDS, or 3) having an initial CD4 cell count of less than 200/mm$^3$ within one year after the date of HIV diagnosis. Early mortality was defined as death from AIDS-related causes within one year of an HIV/AIDS diagnosis. Cases without a death certificate or without being lost to follow-up as of 31 December 2014, were assumed to be alive. Cases who died of overdose drug use or suicide were excluded.

We defined preventable early mortality as the estimated number of AIDS-related deaths within one year of diagnosis attributed to late diagnosis. The number of preventable early mortality equals to the number of observed AIDS-related deaths within one year of diagnosis minus the estimated number of AIDS-related deaths within one year of diagnosis according to the early mortality rate of those who received timely HIV diagnoses.

Statistical analysis
We used SAS software (version 9.4; SAS Institute; Cary, NC) for data analysis and MapInfo Professional software (version 15.0; Pitney Bowes; USA) for maps creation. Descriptive analysis was done for late diagnoses across all cases, including gender, age at HIV diagnosis, marital
status, education level, route of transmission, ethnic
group, and screening sites. Screening sites were catego-
rized into three groups: VCT sites, hospitals, and deten-
centers. Transmission routes were classified into five
groups: heterosexual, homosexual, injection drug
use, sexual contact and injection drug use, and former
paid blood/plasma donation. Odds ratio (OR) was used
to assess the factors associated with late diagnosis by
means of univariate and multivariate logistic regression
models. Variables for which P values were less than 0.05
were considered to be statistically significant.

Results
A total of 563,961 individuals were newly diagnosed
with HIV infection in mainland China during the
period between 1 January 2006 and 31 December
2014. A total of 35,727 subjects were excluded from
this analysis, as 28,544 cases could not be traced after
the initial positive tests and 7183 cases concerned in-
dividuals were under 15 years of age (Fig. 1). Among
the remaining 528,234 individuals, the majority were
male (72.7%), married (50.2%), had attained a middle
school level education or higher (60.8%), heterosexual
(63.2%), and belonged to the Han ethnic group
(74.6%). Most were diagnosed at hospitals (44.7%)
and VCT sites (28.4%) (Table 1).

In this cohort, 179,700 (34.0%) individuals newly diag-
nosed with HIV infection were classified as “late diagno-
sis” cases in accordance with the definition. The late
diagnosis rate decreased from 33.9% in 2006 to 29.7% in
2014 (P < 0.01) (Fig. 2). The proportion of cases of late
diagnosis were more than 55% among four provinces in
2006, three provinces in 2010 and none in 2014 (Fig. 3).

The proportion of cases of late diagnosis was greater
among those who were over 45 years old, married,
farmers or rural laborers, and of Han ethnicity, infected
through heterosexual transmission or former blood/
plasma transfusion, diagnosed at hospitals, (Table 1). In
addition, our results indicated that cases of late diagnosis
increased with an increase in age in all calendar years
during the study period.

As per our results, factors independently associated
with an increased likelihood of late diagnosis were be-
ing male (aOR: 1.15, 95% CI: 1.13–1.17), being in an
older age group (aOR: 3.25, 95% CI: 3.17–3.34 for
45–54 years old; aOR: 2.94, 95% CI: 2.86–3.02 for 55
years old), having acquired HIV infection through
former blood or plasma transfusion (aOR: 4.18, 95%
CI: 4.02–4.35), being of Han ethnicity (aOR: 1.30,
95% CI: 1.28–1.32), being married or living with a
partner (aOR: 1.15, 95% CI: 1.13–1.17), being farmers
(aOR: 1.13, 95% CI: 1.11–1.14), and being tested at
hospitals (aOR: 1.17, 95% CI: 1.15–1.19).

Around 52.0% of newly diagnosed cases (274,552) had
their CD4 cell count results available within one month
of HIV diagnosis (Table 2). This proportion increased
from 19.0% in 2006 to 65.8% in 2014. Furthermore, this
proportion was the lowest (29.7%) among those who
were infected through injection drug use. Those who
were diagnosed at VCT clinics received a timely (within
one month) CD4 cell count testing of 60.9%.

Our results indicate that 76.5% (404,000) of newly
HIV diagnosed individuals received testing for CD4 cell
count within one year of HIV diagnosis (Table 2). Of
these individuals, 32.4% (131,095) had a CD4 cell count
less than 200 cells/mm³. The proportion with a CD4 cell
count test administered within one year increased during
the study period from 35.1% in 2006 to 88.3% in 2014,
and the proportion of CD4 cell count less than 200
cells/mm³ decreased from 42.7% in 2006 to 29.7% in
2014. Those infected through former blood or plasma
transfusion witnessed a high proportion of CD4 cell
count less than 200 cells/mm³. The proportion of CD4
cell count less than 200 cells/mm³ increased with age,
from 13.3% in 15–24 age group to 44.8% in 55+ age
group.

Early mortality and access to ART
Of the 179,700 individuals who received late diagnoses,
excluding 1404 individuals who died of overdose drug
use or suicide, the proportions receiving ART within
one month of diagnosis and within one year of diagnosis
were 30.1 and 65.4%, respectively. The percentage of the
individuals who received late diagnoses, received ART,
and died within one month of diagnosis was 0.51%. The
percentage of the individuals who received late diagnos-
eses, received ART, and died within one year of diagnosis
was 7.4% (Table 3). 17.4% of individuals who received
late diagnoses but did not receive ART died within one
month of diagnosis, and 46.1% of those who received
late diagnoses without ART died within one year of diag-
nosis. Upon further analysis, the early mortality was
20.8% (37,099/178,296) among those who received late
diagnoses and 9.6% (32,626/341,072) among those with
timely diagnoses (P < 0.01).

Among PLHIV who received late diagnoses, the pro-
portion experiencing early mortality declined annually
from 2006 to 2014 with an increase in the proportion re-
ceiving ART (Table 4). The early mortality rates for indi-
viduals who received late diagnoses were 29.5% in 2006
and 14.5% in 2014. At the same time, the treatment
coverage rates for these individuals within one year of
diagnosis were 39.5% in 2006 and 73.9% in 2014. The
treatment coverage rate for those who reported having
had sex with men was highest (82.8%) (p < 0.01), there-
fore, this group also experienced the lowest rate of early
mortality (8.0%) (Table 4).
Estimation of preventable early mortality

Early mortality among those who received timely HIV diagnoses was 9.6%. Basing our assumptions of previous research [30–32], we presumed in our study that 1) early mortality would be reduced to 9.6% if there were no late diagnoses; 2) there would be no effect on deaths occurring more than a year after diagnosis; and 3) there would be no other competing risks. Based on these conjectures, only 17,116 deaths would have been expected from 2006 to 2014 within a year of diagnosis if the diagnosis was timely. That is, 19,983 deaths would have been avoided during this period, compared to the 37,099 deaths actually observed among the group with late HIV diagnoses. Therefore,
| Categories                          | Newly diagnosed (age > 14 years old) | n (%) of Late diagnosis | Unadjusted OR (95%CI) | Adjusted OR (95%CI) |
|------------------------------------|-------------------------------------|-------------------------|-----------------------|---------------------|
| Total                              | 528,234                             | 179,700(34.0)           | _                     | _                   |
| Year of HIV diagnosis              |                                     |                         |                       |                     |
| 2006                               | 26,027                              | 8823(33.9)              | Ref.                  | Ref.                |
| 2007                               | 32,538                              | 11,427(35.1)            | 1.06 (1.02–1.09)      | 1.04 (1.00–1.08)    |
| 2008                               | 40,690                              | 13,734(33.8)            | 0.99(0.96–1.03)       | 0.93(0.89–0.96)     |
| 2009                               | 48,163                              | 17,073(35.4)            | 1.07(1.04–1.11)       | 0.99(0.95–1.02)     |
| 2010                               | 53,375                              | 19,700(36.9)            | 1.14(1.11–1.18)       | 0.99(0.96–1.03)     |
| 2011                               | 67,256                              | 23,944(35.6)            | 1.08(1.05–1.11)       | 0.89(0.86–0.92)     |
| 2012                               | 76,716                              | 26,598(34.7)            | 1.04(1.01–1.07)       | 0.84(0.81–0.87)     |
| 2013                               | 85,516                              | 29,291(34.3)            | 1.02(0.99–1.05)       | 0.82(0.79–0.85)     |
| 2014                               | 97,951                              | 29,110(29.7)            | 0.83(0.80–0.85)       | 0.65(0.63–0.68)     |
| Sex                                |                                     |                         |                       |                     |
| Female                             | 144,013                             | 49,803(34.6)            | Ref.                  | Ref.                |
| Male                               | 384,221                             | 129,897(33.8)           | 0.97(0.95–0.98)       | 1.15(1.13–1.17)     |
| Age groups(years)                  |                                     |                         |                       |                     |
| 15–24                              | 74,796                              | 12,174(16.3)            | Ref.                  | Ref.                |
| 25–34                              | 163,089                             | 44,161(27.1)            | 1.91(1.87–1.95)       | 1.87(1.82–1.91)     |
| 35–44                              | 132,507                             | 51,750(39.1)            | 3.30(3.22–3.37)       | 2.78(2.72–2.85)     |
| 45–54                              | 70,158                              | 32,262(46.0)            | 4.38(4.27–4.49)       | 3.25(3.17–3.34)     |
| 55+                                | 87,684                              | 39,353(44.9)            | 4.19(4.09–4.29)       | 2.94(2.86–3.02)     |
| Marital status                     |                                     |                         |                       |                     |
| Single, divorced, or widowed       | 256,895                             | 74,319(28.9)            | Ref.                  | Ref.                |
| Married or lives with partner       | 264,977                             | 104,087(39.3)           | 1.59(1.57–1.61)       | 1.12(1.11–1.13)     |
| Education                          |                                     |                         |                       |                     |
| Middle school or more              | 331,210                             | 111,091(33.5)           | Ref.                  | Ref.                |
| Primary school or less             | 191,811                             | 67,212(35.0)            | 1.07(1.06–1.08)       | 0.87(0.86–0.89)     |
| Occupation                         |                                     |                         |                       |                     |
| Other                              | 278,138                             | 84,141(30.3)            | Ref.                  | Ref.                |
| Farmer or rural laborer            | 250,096                             | 95,559(38.2)            | 1.43(1.41–1.44)       | 1.13(1.11–1.14)     |
| Ethnic group                       |                                     |                         |                       |                     |
| Other                              | 134,406                             | 35,356(26.3)            | Ref.                  | Ref.                |
| Han                                | 393,828                             | 144,344(36.7)           | 1.62(1.60–1.64)       | 1.30(1.28–1.32)     |
| Route of HIV infection             |                                     |                         |                       |                     |
| Heterosexual                       | 333,753                             | 126,658(37.9)           | Ref.                  | Ref.                |
| Homosexual                         | 85,252                              | 20,891(24.5)            | 0.53(0.52–0.54)       | 0.71(0.70–0.73)     |
| Injection drug use                 | 73,834                              | 14,111(19.1)            | 0.39(0.38–0.39)       | 0.63(0.61–0.64)     |
| Sexual contact and injection drug  | 5257                                | 1147(21.8)              | 0.46(0.43–0.49)       | 0.71(0.66–0.76)     |
| Blood or plasma transfusion        | 16,767                              | 12,910(77.0)            | 5.47(5.28–5.68)       | 4.18(4.02–4.35)     |
| Sites of diagnosis                 |                                     |                         |                       |                     |
| VCT centers                        | 150,157                             | 54,260(36.1)            | Ref.                  | Ref.                |
| Hospitals                          | 236,047                             | 97,220(41.2)            | 1.24(1.22–1.25)       | 1.17(1.15–1.19)     |
| Detention centers                  | 43,231                              | 5087(11.8)              | 0.24(0.23–0.24)       | 0.35(0.34–0.37)     |
| others                             | 98,799                              | 23,133(23.4)            | 0.54(0.53–0.55)       | 0.59(0.58–0.61)     |
the current burden of early mortality would be reduced by about 53.9%.

Discussion

It has been thirty years since HIV testing first became available [33]. Despite the decades of availability of testing, it was estimated that at least one-fourth of PLHIV worldwide were unaware of their infection [24, 34–39], and that this ratio could be even higher in China [24]. Our results indicate that promoting timely diagnosis and treatment provided a survival advantage to PLHIV, and that almost 54% of deaths that occurred within one year of HIV diagnosis could thus be prevented. Our study expanded upon the existing literature [16, 32, 37, 40, 41] by evaluating late diagnoses among all HIV cases identified between 2006 and 2014 in China, by assessing and mapping the trend of late diagnosis over time and by evaluating factors associated with late diagnosis among HIV cases in China.

In our study, 34.0% of HIV cases were considered to have received late diagnoses between 2006 and 2014. The late diagnosis rate fluctuated from 2006 to 2014, but slightly decreased from 36.9% in 2010 to 29.7% in 2014 (P < 0.01). This declining could be due to the implementation of the provider-initiated HIV testing and counseling (PITC) strategy since 2009. After the initiating of PITC, the HIV testing was significantly scaled up in most of provinces in China [37, 38, 42]. The scaling up of HIV self-testing in China could be another reason for this phenomenon. For example, around 30% of MSM in China self-reported that they ever self-tested in 2016 [36].

The propensity to receive late HIV testing was greater for older people, those who had acquired HIV infection through former blood or plasma transfusion or heterosexual behaviors, individuals of Han ethnicity, married individuals, and farmers. These results are consistent with the findings of previous studies [31, 43], with the exception of some studies in the U.S. indicated that younger people was more likely to receive late testing [44, 45]. In recent years, spouses’ and regular partners’ testing was scaled up in China, because of a series of national and provincial laws, regulations, and policy initiatives.

| Categories          | Newly diagnosed (age > 14 years old) | n (%) of Late diagnosis | Unadjusted OR (95%CI) | Adjusted OR (95%CI) |
|---------------------|-------------------------------------|-------------------------|-----------------------|---------------------|
| Migrant population  | No                                  | 402,155                 | 143,160(35.6)         | Ref.                |
|                     | Yes                                 | 126,079                 | 36,540(29.0)          | 0.74(0.73–0.75)     | 0.94(0.93–0.96)     |

*Migrant population: people migrated from one county to another county and stay there for at least six months.

Fig. 2 Proportions of individuals diagnosed late in different calendar years of diagnosis (X axis: calendar year of diagnosis; Y axis: proportion of late diagnosis)
Fig. 3 Proportions of individuals diagnosed late in different calendar years of diagnosis among 31 provinces in China (a: year of 2006, b: year of 2010, c: year of 2014)
The majority of late diagnoses occurred among those who were infected with HIV through heterosexual behaviors. It indicated that there might have been a prolonged period of transmission risk to their sexual partners. Strategies, promoting rapid HIV testing at primary level of health institutions, promoting HIV self-testing, and increasing collaboration with community based organizations (CBOs), should be further implemented. Also, the risk of late diagnosis was significantly higher for those who were infected through former blood or plasma transfusion. Illegal paid plasma donation was prominent in central China in the 1990s [26, 46, 47]. Most of these PLHIV did not seek testing due to societal discrimination and stigma against HIV. As a result, they were diagnosed with HIV only after they experienced symptoms. Most of these people are located in four provinces in central China, as shown in Fig. 3.

However, the proportion of late testing has decreased among men who have sex with men (MSM) and injection drug users in recent years. This finding may have been due to ongoing intervention programs that promoted testing in these high risk groups [48, 49], such as methadone maintenance treatment (MMT) for injection drug users and free HIV testing for MSM provided by CBOs and VCT clinics. Similar results have been found in other studies [45].

Individuals who present at an advanced stage of immunosuppression are at high risk of clinical events and death and are more likely to have a poor response when they start ART [50, 51]. The proportion of people receiving late diagnoses among newly diagnosed individuals remained at more than 30% between 2006 and 2013. However, this proportion has been in decline since 2010. In an era where effective and free testing and free treatment options are available in China, it is alarming that there is a substantial proportion of people were late diagnosed, and they are at higher risk of early death. A records-based retrospective cohort study in China found that the highest mortality rates for AIDS-related death and all-cause death were found in the first year

Table 2 Initial CD4 cell counts after diagnosed of HIV newly diagnosed individuals in China between 2006 and 2014 (N = 528,234)

| Characteristic | Newly diagnosed (age > 14 years old) | Initial CD4 cell count within one month | Initial CD4 cell count within one year | Initial CD4 cell counts < 200 cell/ul within one year |
|----------------|--------------------------------------|----------------------------------------|---------------------------------------|-----------------------------------------------------|
| Year of HIV diagnosis | n | % | n | % | n | % |
| 2006 | 26,027 | 4950 | 19.0 | 9129 | 35.1 | 3901 | 42.7 |
| 2007 | 32,538 | 8856 | 27.2 | 15,621 | 48.0 | 6282 | 40.2 |
| 2008 | 40,690 | 14,475 | 35.6 | 23,979 | 58.9 | 8491 | 35.4 |
| 2009 | 48,163 | 20,327 | 42.2 | 32,083 | 66.6 | 11,321 | 35.3 |
| 2010 | 53,375 | 25,110 | 47.0 | 40,073 | 75.1 | 13,511 | 33.7 |
| 2011 | 67,256 | 35,950 | 53.5 | 54,378 | 80.9 | 18,002 | 33.1 |
| 2012 | 76,716 | 45,550 | 59.4 | 66,064 | 86.1 | 20,444 | 30.9 |
| 2013 | 85,518 | 54,931 | 64.2 | 76,191 | 89.1 | 23,474 | 30.8 |
| 2014 | 97,951 | 64,403 | 65.8 | 86,482 | 88.3 | 25,669 | 29.7 |
| Route of HIV infection | | | | | | |
| Heterosexual | 333,753 | 183,602 | 55.0 | 264,332 | 79.2 | 96,527 | 29.7 |
| Homosexual | 85,252 | 57,299 | 67.2 | 78,895 | 92.5 | 15,515 | 19.7 |
| Injection drug use | 73,834 | 21,958 | 29.7 | 40,713 | 55.1 | 9168 | 22.5 |
| Sexual contact and injection drug use | 5257 | 1760 | 33.5 | 3257 | 62.0 | 777 | 23.9 |
| Blood or plasma transfusion | 16,767 | 7006 | 41.8 | 11,833 | 70.6 | 7142 | 60.4 |
| Sites of diagnosis | | | | | | |
| VCT centers | 150,157 | 91,425 | 60.9 | 124,603 | 83.0 | 39,141 | 31.4 |
| Hospitals | 236,047 | 118,702 | 50.3 | 176,834 | 74.9 | 73,114 | 41.3 |
| Detention centers | 43,231 | 12,397 | 28.7 | 23,395 | 54.1 | 3196 | 13.7 |
| others | 98,799 | 52,028 | 52.7 | 79,168 | 80.1 | 15,644 | 19.8 |
| Total | 528,234 | 274,552 | 52.0 | 404,000 | 76.5 | 131,095 | 32.4 |
of follow up after HIV diagnosis [52]. This phenomenon could be explained by the fact that about half of the participating cases had already progressed to AIDS before being identified, progression to AIDS was one of the strongest risk factors for AIDS-related death, with an aHR of 7.42 [52].

Individuals who present at an advanced stage of immunosuppression are at high risk of AIDS related diseases and death as well as more likely to have a poorer response to ART [36, 53]. Both HIV testing and ART have been free for PLHIV in China since 2003 [54]. In spite of this policy, our results indicate that as many as 30% of all newly diagnosed individuals received late diagnoses. Shortening the time from infection to measurement of CD4 cell counts could be an important window for early treatment. We infer that the time from infection to CD4 measurement is a useful indicator for monitoring delays in access to HIV medical care among newly diagnosed PLHIV [55]. In our analysis, 52.0% of newly diagnosed individuals had their CD4 cell counts available within one month of HIV diagnosis. This proportion increased from 19.0% in 2006 to 65.8% in 2014.

| Duration of time from diagnosis | Initial CD4 counts | ON ART | NO ART |
|-------------------------------|--------------------|--------|--------|
|                               | N | No. of death | % of death | N | No. of death | % of death |
| One month                     |   |             |           |   |             |           |
| 0–49                          | 33,897 | 325 | 0.96 | 15,344 | 2449 | 15.96 |
| 50–99                         | 19,220 | 63  | 0.33 | 7153  | 516  | 7.21  |
| 100–199                       | 37,747 | 44  | 0.12 | 13,934 | 330  | 2.37  |
| 200–349                       | 17,685 | 14  | 0.08 | 6718  | 81   | 1.21  |
| 350–499                       | 5135  | 3   | 0.06 | 3301  | 32   | 0.97  |
| 500–                           | 2041  | 0   | 0.00 | 1977  | 10   | 0.51  |
| No CD4 test                   | 848  | 142 | 16.75 | 13,269 | 7316 | 55.02 |
| subtotal                      | 116,573 | 591 | 0.51 | 61,723 | 10,734 | 17.39 |
| Three months                  |   |             |           |   |             |           |
| 0–49                          | 33,897 | 1551 | 4.58 | 15,344 | 5705 | 37.18 |
| 50–99                         | 19,220 | 390 | 2.03 | 7153  | 1399 | 19.56 |
| 100–199                       | 37,747 | 283 | 0.75 | 13,934 | 1000 | 7.18  |
| 200–349                       | 17,685 | 61  | 0.34 | 6718  | 201  | 2.99  |
| 350–499                       | 5135  | 15  | 0.29 | 3301  | 77   | 2.33  |
| 500–                           | 2041  | 3   | 0.15 | 1977  | 34   | 1.72  |
| No CD4 test                   | 848  | 398 | 46.93 | 13,296 | 9674 | 72.76 |
| subtotal                      | 116,573 | 2701 | 2.32 | 61,723 | 18,090 | 29.31 |
| Six months                    |   |             |           |   |             |           |
| 0–49                          | 33,897 | 2950 | 8.70 | 15,344 | 7963 | 51.90 |
| 50–99                         | 19,220 | 880 | 4.58 | 7153  | 2253 | 31.50 |
| 100–199                       | 37,747 | 678 | 1.80 | 13,934 | 1684 | 12.09 |
| 200–349                       | 17,685 | 147 | 0.83 | 6718  | 359  | 5.34  |
| 350–499                       | 5135  | 39  | 0.76 | 3301  | 157  | 4.76  |
| 500–                           | 2041  | 14  | 0.69 | 1977  | 70   | 3.54  |
| No CD4 test                   | 848  | 560 | 66.04 | 13,296 | 10,838 | 81.51 |
| subtotal                      | 116,573 | 5268 | 4.52 | 61,723 | 23,324 | 37.79 |
| Twelve months                 |   |             |           |   |             |           |
| 0–49                          | 33,897 | 4521 | 13.34 | 15,344 | 9796 | 63.84 |
| 50–99                         | 19,220 | 1520 | 7.91 | 7153  | 3100 | 43.34 |
| 100–199                       | 37,747 | 1385 | 3.67 | 13,934 | 2654 | 19.05 |
| 200–349                       | 17,685 | 361 | 2.04 | 6718  | 628  | 9.35  |
| 350–499                       | 5135  | 107 | 2.08 | 3301  | 307  | 9.30  |
| 500–                           | 2041  | 53  | 2.60 | 1977  | 141  | 7.13  |
| No CD4 test                   | 848  | 690 | 81.37 | 13,296 | 11,836 | 89.02 |
| subtotal                      | 116,573 | 8637 | 7.41 | 61,723 | 28,462 | 46.11 |

*aThose who died of overdose drug use or suicide were excluded*
Table 4  Access to ART and early mortality among late diagnosis individuals within one year of diagnosis between 2006 and 2014 (N=178,296)

| Characteristics                      | Late diagnosis (age>14 years old)* | N (% of access to ART within one month) | N (% of access to ART within one year) | N (% of died after receiving ART) | $\chi^2$ | P-value |
|--------------------------------------|------------------------------------|----------------------------------------|----------------------------------------|-----------------------------------|--------|--------|
| Year of HIV diagnosis                |                                    |                                        |                                        |                                   |        |        |
| 2006                                 | 8675                               | 1436(16.6)                             | 3429(39.5)                             | 267(7.8)                          | 141.52 | <0.01  |
| 2007                                 | 11252                              | 2105(18.7)                             | 5126(45.6)                             | 341(6.7)                          |        |        |
| 2008                                 | 13535                              | 3051(22.5)                             | 7387(54.6)                             | 568(7.7)                          |        |        |
| 2009                                 | 16874                              | 3906(23.1)                             | 9527(56.5)                             | 621(6.5)                          |        |        |
| 2010                                 | 19532                              | 4498(23.0)                             | 12021(61.5)                            | 679(5.6)                          |        |        |
| 2011                                 | 23741                              | 6383(26.9)                             | 16355(68.9)                            | 1076(6.6)                         |        |        |
| 2012                                 | 26445                              | 8524(32.2)                             | 19038(72.0)                            | 1495(7.9)                         |        |        |
| 2013                                 | 29192                              | 11068(37.9)                            | 22212(76.1)                            | 1897(8.5)                         |        |        |
| 2014                                 | 29050                              | 12668(43.6)                            | 21478(73.9)                            | 1693(7.9)                         |        |        |
| Sex                                  |                                    |                                        |                                        |                                   |        |        |
| Female                               | 49561                              | 15132(30.5)                            | 32806(66.2)                            | 1959(6.0)                         | 137.54 | <0.01  |
| Male                                 | 128735                             | 38507(29.9)                            | 83767(65.1)                            | 6678(8.0)                         |        |        |
| Age group (years)                    |                                    |                                        |                                        |                                   |        |        |
| 15-24                                | 12082                              | 3107(25.7)                             | 8305(68.7)                             | 317(3.8)                          | 871.48 | <0.01  |
| 25-34                                | 43688                              | 12146(27.8)                            | 28734(65.8)                            | 1436(6.0)                         |        |        |
| 35-44                                | 51244                              | 15499(30.2)                            | 33684(65.7)                            | 2430(7.2)                         |        |        |
| 45-54                                | 32084                              | 10846(33.8)                            | 21947(68.4)                            | 1832(8.3)                         |        |        |
| 55+                                  | 39198                              | 12041(30.7)                            | 23903(61.0)                            | 2622(11.0)                        |        |        |
| Marital status                       |                                    |                                        |                                        |                                   |        |        |
| Single, divorced, or widowed         | 73626                              | 20957(28.5)                            | 48061(65.3)                            | 3411(7.1)                         | 11.08  | <0.01  |
| Married or lives with partner        | 103411                             | 32483(31.4)                            | 67970(65.7)                            | 5177(7.6)                         |        |        |
| Education                            |                                    |                                        |                                        |                                   |        |        |
| Middle school or more                | 110338                             | 34898(31.6)                            | 77177(69.9)                            | 4792(6.2)                         | 488.54 | <0.01  |
| Primary school or less               | 66599                              | 18585(27.9)                            | 39012(58.6)                            | 3826(9.8)                         |        |        |
| Occupation                           |                                    |                                        |                                        |                                   |        |        |
| Other                                | 83510                              | 25305(30.3)                            | 57787(69.2)                            | 3130(5.4)                         | 663.26 | <0.01  |
| Farmer or rural laborer              | 94786                              | 28334(29.9)                            | 58786(62.0)                            | 5507(9.4)                         |        |        |
| Ethnic group                         |                                    |                                        |                                        |                                   |        |        |
| Others                               | 34969                              | 9013(25.8)                             | 19866(56.8)                            | 1335(6.7)                         | 16.57  | <0.01  |
| Han                                  | 143327                             | 44626(31.1)                            | 96707(67.5)                            | 7302(7.6)                         |        |        |
| Route of HIV infection               |                                    |                                        |                                        |                                   |        |        |
| Heterosexual                         | 126054                             | 40124(31.8)                            | 83978(66.6)                            | 6547(7.8)                         | 622.49 | <0.01  |
| Homosexual                           | 20832                              | 6951(33.4)                             | 17167(82.4)                            | 646(3.8)                          |        |        |
| Injection drug use                   | 13531                              | 1955(14.4)                             | 5809(42.9)                             | 372(6.4)                          |        |        |
| Sexual contact and IDU               | 1102                               | 245(22.2)                              | 560(50.8)                              | 31(5.5)                           |        |        |
| Blood or plasma transfusion          | 12841                              | 3722(29.0)                             | 7457(58.1)                             | 917(12.3)                         |        |        |
| Sites of diagnosis                   |                                    |                                        |                                        |                                   | 681.88 | <0.01  |
| VCT centers                          | 53825                              | 17809(33.1)                            | 36452(67.7)                            | 2346(6.4)                         |        |        |
| Hospitals                            | 96608                              | 29659(30.7)                            | 62791(65.0)                            | 5683(9.1)                         |        |        |
| Detention centers                    | 4859                               | 197(4.1)                               | 1563(32.2)                             | 62(4.0)                           |        |        |
| others                               | 23004                              | 5974(26.0)                             | 15767(68.5)                            | 546(3.5)                          |        |        |
It is very important for late diagnosed individuals to receive CD4 cell count testing immediately, so that they can receive referrals for timely ART and thus reduce their risk of death. In our study, this proportion of cases received ART within one month after the diagnoses increased from 16.6% in 2006 to 43.6% in 2014. The average proportion of having CD4 counts within one year was 76% from 2006 to 2014. The causes of not having CD4 counts testing within one year included death before having CD4 counts, lost to follow up, and inconvenience to access to CD4 count test. To shorten the time to CD4 cell count testing and to improve access to regular testing and treatment, efforts were taken in the past few years to dramatically improve referrals and integration of patient tracking between the health facilities responsible for patients follow up, CD4 cell count testing, and ART delivery [56].

Our analysis suggests that groups at high risk of late diagnosis should be targeted for appropriate public health intervention and encouraged to seek earlier treatment. Scaling up HIV testing is one of the important strategies in implementing this goal. This strategy may bring out a greater proportion of hidden individuals infected with HIV [57]. Another strategy would be to consider population-wide screening for HIV, such as for patients in hospitals. In the U.S., the CDC recommends routine HIV counseling and testing in healthcare settings for patients aged 13–64 years, unless the local HIV prevalence is known to be less than 0.1% [1].

There are some limitations to consider while interpreting our findings. Firstly, 2.3% (12,352/528,234) individuals were lost to follow-up after HIV diagnoses, and then CD4 cell counts data or having WHO stage 3 or 4 of them were not available at diagnosis. Thus, it is possible that some individuals with AIDS may have been misclassified as having HIV. However, the resulting misclassification will be non-differential and might bias the estimates towards the null, because the proportion of individuals misclassified does not depend on the individual with respect to other variables on the analysis [58]. Secondly, our results couldn’t assess differences in mortality in late diagnosed individuals who access to ART based on ART regimen. It needs further research.

**Conclusion**

Even with these limitations, our results still indicate that it is important to increase the accessibility of HIV testing services. Routine testing for most individuals has been recommended as a cost-effective strategy and efforts to promote such testing should be developed [40, 53].

**Table 4** Access to ART and early mortality among late diagnosis individuals within one year of diagnosis between 2006 and 2014 (N=178,296) (Continued)

| Characteristics | Late diagnosis (age>14 years old)* | N (% of access to ART within one month) | N (% of access to ART within one year) | N (% of died after receiving ART) | χ² | P-value [b] |
|-----------------|------------------------------------|----------------------------------------|----------------------------------------|----------------------------------|----------------|--------------|
| Migrant population a |                                    |                                        |                                        |                                  | 10.03 | <0.01       |
| No              | 142108                             | 43658(30.7)                            | 93717(65.9)                            | 7056(7.5)                        |      |              |
| Yes             | 36188                              | 9981(27.6)                             | 22856(63.2)                            | 1581(6.9)                        |      |              |
| Initial CD4+ cell count |                                    |                                        |                                        |                                  | 10298.66 | <0.01       |
| 0-49            | 49241                              | 18191(36.9)                            | 33897(68.8)                            | 4521(13.3)                       |      |              |
| 50-99           | 26373                              | 9778(37.1)                             | 19220(72.9)                            | 1520(7.9)                        |      |              |
| 100-199         | 51681                              | 17268(33.4)                            | 37747(73.0)                            | 1385(3.7)                        |      |              |
| 200-349         | 24403                              | 6167(25.3)                             | 17685(72.5)                            | 361(2.0)                         |      |              |
| 350-499         | 8436                               | 1177(14.0)                             | 5135(60.9)                             | 107(2.1)                         |      |              |
| 500-             | 4018                               | 476(11.8)                              | 2041(50.8)                             | 53(2.6)                          |      |              |
| No CD4 records | 14144                              | 582(4.1)                               | 848(6.0)                               | 690(81.4)                        |      |              |
| Total           | 178296                             | 53639(30.1)                            | 116573(65.4)                           | 8637(7.4)                        |      |              |

[a] Those who died of overdose drug use or suicide were excluded.  
[b] The proportion of those who died after ART within one year is compared by different characteristics.
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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
HT, YM, WT, JH, JX, and JL contributed to the study design and authored the study. HT and YM, conceived and designed the study. HT analyzed the data. HT, YM, and WT wrote the initial draft of this manuscript. HT and YM had full access to all of the data in the study and YM had responsibility for the decision to submit the final manuscript for publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was a secondary data analysis using existing Chinese government HIV/AIDS CRIMS data. Therefore, no additional study specific informed consent was necessary for this current study. Patient records and information were de-identified prior to analysis. This study protocol was reviewed and approved by the Institutional Review Board of the National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention (approval #X160310409).

Competing interests
The authors declare that they have no competing interests.

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