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Immediate Antiretroviral Therapy Decreases Mortality Among Patients With High CD4 Counts in China: A Nationwide, Retrospective Cohort Study

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Background. Clinical trials have demonstrated that immediate initiation of antiretroviral therapy (ART) reduces AIDS-related morbidity and mortality. We tested the hypothesis that initiating ART ≤30 days after human immunodeficiency virus (HIV) diagnosis would be associated with reduced mortality among people living with HIV (PLWH) with CD4 counts >500 cells/μL.

Methods. PLWH enrolled in the Chinese National HIV Information System between January 2012 and June 2014 with CD4 counts >500 cells/μL were followed for 12 months. Cox proportional hazards model was used to determine hazard ratios (HRs) for PLWH who initiated ART after HIV diagnosis. ART initiation was treated as a time-dependent variable.

Results. We enrolled 34 581 PLWH with CD4 >500 cells/μL; 1838 (5.3%) initiated ART ≤30 days after diagnosis (immediate ART group), and 19 deaths were observed with a mortality rate of 1.04 per 100 person-years (PY). Fifty-eight deaths were documented among the 5640 PLWH in the delayed ART group with a mortality rate of 2.25 per 100 PY. There were 713 deaths among the 27 103 PLWH in the no ART group with a mortality rate of 2.39 per 100 PY. After controlling for potential confounding factors, ART initiation at ≤30 days (adjusted HR, 0.37 [95% confidence interval, .23–.58]) was a statistically significant protective factor.

Conclusions. We found that immediate ART is associated with a 63% reduction in overall mortality among PLWH with CD4 counts >500 cells/μL in China, supporting the recommendation to initiate ART immediately following HIV diagnosis.

Keywords. HIV/AIDS; antiretroviral therapy; treatment initiation; CD4 count; mortality.

Over the past 2 decades, combination antiretroviral therapy (ART) has been a cornerstone of the response to the epidemic of human immunodeficiency virus (HIV) infection that causes AIDS [1–3]. The scale-up of ART has resulted in substantial reductions in AIDS-related mortality and morbidity, as well as reduced HIV transmission [4–8]. Nevertheless, less than half of the estimated 36.7 million people living with HIV (PLWH) were receiving ART in 2015 [9].

Historically, there has been an early consensus that PLWH who had an AIDS-defining illness should initiate ART immediately. For those who had not yet progressed to AIDS, the World Health Organization (WHO) has recommended that $CD4^+$ T-lymphocyte thresholds guide the timing of ART initiation [10]. However, observational studies, predominantly carried out in resource-rich settings [11], have found that ART initiation among PLWH with CD4 counts >500 cells/μL was associated with substantial clinical benefits, and this has now been confirmed by prospective randomized trials [12–15]. Taken together with the results of the HPTN 052 trial [7, 8], showing the sustained ability of ART to prevent sexual transmission of HIV, these findings led the WHO to revise their recommendation in September 2015, now completely removing the CD4 count threshold, such that ART is globally recommended for all PLWH [16].

Standard of care for all those diagnosed with HIV infection in China includes free CD4 testing each year, with the first CD4 test offered soon after diagnosis. From 2008 to 2014, the primary criterion for entry into the Chinese National Free Antiretroviral Treatment Program (NFATP) was CD4 count ≤350 cells/μL. During this time, exceptions to the CD4 threshold of ≤350 cells/μL in the NFATP included patients with coinfections, and prevention of mother-to-child transmission [17]. In 2011, the NFATP added a recommendation

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that ART be offered to all PLWH in serodiscordant relationships, regardless of CD4 cell count [17]. In 2012, a special national project for the "Prevention and Treatment of Major Infectious Diseases" was launched, wherein the National Center for AIDS/STD Control and Prevention (NCAIDS) of the Chinese Center for Disease Control and Prevention (China CDC) implemented a series of cluster-randomized trials among key populations, including men who have sex with men, serodiscordant couples, people who inject drugs, and commercial sex workers. The targeted outcome was early identification of HIV infection and immediate ART initiation regardless of CD4 cell count. Thus, PLWH participating in the study were exempt from the standard-of-care CD4 threshold for ART initiation.

The primary aim of the present study was to examine mortality and its determinants among a cohort of newly diagnosed PLWH with first CD4 count >500 cells/μL. Participants were followed for 1 year to examine the impact of immediate ART initiation on mortality among PLWH with high CD4 counts, compared to those with delayed ART initiation and to those who remained ART naive. Secondarily, we also sought to describe causes of death within our cohort.

METHODS

Study Design and Setting

This nationwide, observational cohort study was designed to examine mortality among patients who received confirmed diagnoses of HIV infection between 1 January 2012 and 30 June 2014 and had a CD4 count >500 cells/μL. Mortality and factors associated with mortality were assessed at 1 year. A flow diagram illustrating the study design is shown in Figure 1. The treatment setting was China's NFATP. This program, as well as treatment regimens (eg, drug combinations used, dosage, and administration) and follow-up protocols for enrolled patients, have been described previously [17, 18].

Data Source

Data were extracted from China's Web-based national database for real-time collection and maintenance of information related to the HIV epidemic. This system, called the HIV/AIDS Comprehensive Response Information Management System (CRIMS), has been described elsewhere [19–21]. Because screening for inclusion was nationwide and included all identified cases, sample size was not initially defined.

Data Collection and Inclusion Criteria

All CRIMS records of persons with a confirmed diagnosis of HIV infection between 1 January 2012 and 30 June 2014 were extracted and then further screened for study eligibility criteria. In addition to a confirmed new HIV diagnosis, PLWH were included if they were 18 years or older at the time of diagnosis, had a CD4 test result within 1 year of diagnosis, had baseline (pre-ART) CD4 count of >500 cells/μL, and had reported having acquired HIV through heterosexual contact, male-to-male sexual contact, or injection drug use. These transmission

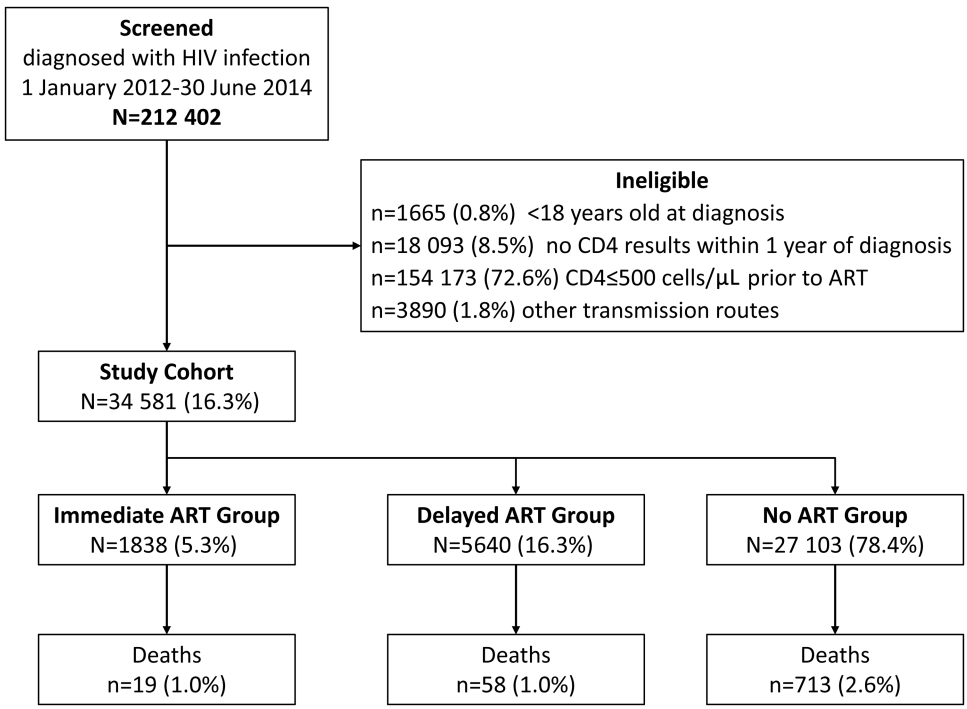

Figure 1. Flow diagram depicting study design and development of the cohort. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

routes accounted for >90% of newly diagnosed HIV infections in China during this time period [22].

All eligible records were extracted and de-identified. Each study participant was followed from the date of their first CD4 test for 12 months afterward or the date of death, whichever came first. As illustrated in Figure 1, participants were stratified by timing of ART initiation relative to the date of confirmed HIV diagnosis (≤30 days after HIV diagnosis referred to as the immediate ART group; >30 days after HIV diagnosis referred to as the delayed ART group; and PLWH who did not start ART within 1 year referred to as the no ART group).

Mortality and Causes of Death

The main outcome measure was all-cause mortality. Dates and causes of death were obtained from clinical records. AIDS-related causes of death were defined by China CDC medical guidelines [23]. Non-AIDS-related causes of death included all other causes.

Statistical Analysis

Continuous variables are presented using median and interquartile range (IQR), and categorical variables are presented using number and percentage. Because of the very large number of patients in our cohort, even very small differences between subgroups would likely result in *P* values reaching statistical significance. However, these small differences would not necessarily be meaningful. Therefore, we focused only on differences of ≥5% between groups being compared.

Observed time, in person-years (PY), was calculated for participants who contributed to the study observation. As the median time interval between confirmed HIV diagnosis and first CD4 test was only 14 days (IQR, 3–57 days), CD4 test date was selected as the start of observed time. Thus, observed time was calculated as the difference between the date of first CD4 test and the date of death or the end of the follow-up period, whichever came first. Mortality rate was calculated as the sum of deaths divided by the sum of observed time in PY. Due to survival bias, patients who accepted ART were always alive before ART initiation. Thus, ART status was treated as a time-dependent variable, meaning that those who accepted ART were a part of the no ART group until ART initiation. Individuals contributed person-time (and deaths) to the immediate ART group after they began ART, provided ART initiation occurred within 30 days of the start. Individuals contributed person-time to the delayed ART group after they began ART, provided ART initiation occurred after 30 days from the start but before 1 year. A multivariate Cox proportional hazards regression model was constructed to assess hazard ratios (HRs) for the study variable ART status, and for demographic variables and HIV clinical variables. The immediate ART variable in the regression model was considered time dependent. That is, it was set to 0 before ART initiation, and to 1 after ART initiation, provided it occurred before the end of day 30. Similarly, the delayed ART variable was set to 0 before ART initiation, and to 1 after ART initiation, provided it occurred after day 30, but within 1 year. Adjusted HRs for the study variable were generated to identify prognostic risk of death by controlling potential confounding bias caused by demographic variables and HIV clinical variables.

All *P* values presented are 2-sided, and $P < .05$ was considered statistically significant. All analyses were performed using SAS software version 9.1.3 (SAS Institute).

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Review Board of NCAIDS, China CDC. As patients entering CRIMS sign informed consent at time of enrollment, no further informed consent was required for this study. All patient records were de-identified prior to data analysis.

RESULTS

A full 212 402 individual records with a date of confirmed HIV diagnosis between 1 January 2012 and 30 June 2014 were available for the study. A total of 34 581 individuals (16.3%) met the eligibility criteria and were included in the final study cohort. Development of the cohort is illustrated in Figure 1.

Characteristics of the Cohort

Characteristics of the entire study cohort, as well as individual subgroups thereof, are shown in Table 1. The median age of patients in the cohort was 32 years (IQR, 25–42 years). A majority were male (75.0%), Han Chinese (72.2%), had junior middle school education or less (63.7%), were single, divorced, or widowed (60.8%), and self-reported acquisition of HIV infection via heterosexual contact (59.9%). Median baseline CD4 count was 616 cells/μL (IQR, 549–732 cells/μL).

Characteristics of Groups Stratified by Timing of ART Initiation

Among 34 581 PLWH, 1838 (5.3%) initiated ART within 30 days of diagnosis and were included in the immediate ART group and 5640 (16.3%) initiated ART >30 days after diagnosis and were included in the delayed ART group. The remaining 27 103 PLWH (78.4%) formed the no ART group. A larger proportion of PLWH in the immediate ART group were female (36.9% vs 28.1% for the delayed ART group and 23.6% for the no-ART group), ethnic minorities (36.0% vs 28.6% and 27.1%), less well educated (junior middle school or less: 72.0% vs 64.4% and 63.0%), married or cohabitating (57.4% vs 49.8% and 35.8%), and reported heterosexual contact as their mode of HIV acquisition (76.7% vs 64.1% and 57.9%).

Mortality and Causes of Death

Deaths and mortality rates are shown in Table 2. The 34 581 PLWH in the study cohort were followed from the date of their first CD4 test until 1 year after or death, whichever was first,

Table 1. Baseline Characteristics of the Entire Study Cohort and of Each Subgroup Based on Antiretroviral Therapy Timing After Confirmed Human Immunodeficiency Virus Diagnosis

Characteristics	Entire Study Cohort	ART Timing After Confirmed HIV Diagnosis		
		Immediate ART (≤30 d)	Delayed ART (>30 d)	No ART (>1 y)
Total	34 581 (100.0)	1838 (100.0)	5640 (100.0)	27 103 (100.0)
Age, y				
Median (IQR)	32 (25–42)	34 (27–46)	33 (26–45)	31 (25–41)
18–29	14 771 (42.7)	653 (35.5)	2110 (37.4)	12 008 (44.3)
30–49	14 976 (43.3)	816 (44.4)	2565 (45.5)	11 595 (42.8)
≥50	4834 (14.0)	369 (20.1)	965 (17.1)	3500 (12.9)
Sex				
Male	25 927 (75.0)	1160 (63.1)	4058 (72.0)	20 709 (76.4)
Female	8654 (25.0)	678 (36.9)	1582 (28.1)	6394 (23.6)
Ethnicity				
Han	24 969 (72.2)	1176 (64.0)	4029 (71.4)	19 764 (72.9)
Other	9612 (27.8)	662 (36.0)	1611 (28.6)	7339 (27.1)
Education level				
Junior middle school or less	22 039 (63.7)	1323 (72.0)	3630 (64.4)	17 086 (63.0)
Senior middle school or higher	12 542 (36.3)	515 (28.0)	2010 (35.6)	10 017 (37.0)
Marital status				
Single, divorced, or widowed	21 019 (60.8)	783 (42.6)	2829 (50.2)	17 407 (64.2)
Married or cohabiting	13 562 (39.2)	1055 (57.4)	2811 (49.8)	9696 (35.8)
Transmission route				
Heterosexual contact	20 713 (59.9)	1409 (76.7)	3615 (64.1)	15 689 (57.9)
Male-to-male sexual contact	10 167 (29.4)	348 (18.9)	1674 (29.7)	8145 (30.1)
Injecting drug use	3701 (10.7)	81 (4.4)	351 (6.2)	3269 (12.1)
Baseline CD4 count, cells/μL				
Median (IQR)	616 (549–732)	596 (538–694)	594 (540–692)	623 (552–744)
Time from diagnosis to CD4 test, d				
Median (IQR)	14 (3–57)	6 (0–20)	11 (1–39)	18 (4–65)
Time from CD4 to ART, d				
Median (IQR)		10 (4–18)	197 (109–283)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral treatment; HIV, human immunodeficiency virus; IQR, interquartile range.

resulting in a total observed time of 34 188 PY. Seven hundred ninety deaths of 34 581 (2.3%) were documented, for an overall mortality rate of 2.31 per 100 PY.

Among the 1838 PLWH in the immediate ART group, 19 deaths were observed within 1828 PY of observed time, for a mortality rate of 1.04 per 100 PY. Fifty-eight deaths were documented among the 5640 PLWH in the delayed ART group within 2583 PY of observed time, for a mortality rate of 2.25 per 100 PY. Finally, 713 deaths were documented among the 27 103 PLWH in the no ART group within 29 778 PY of observed time, for a mortality rate of 2.39 per 100 PY.

The causes of death are presented in Table 3. Causes of death for a majority of the 790 PLWH were documented as non-AIDS-related complications (76.3%). A further 8.6% of PLWH had no cause of death documented or an unclassified cause of death listed in their record. AIDS-related complications were identified as the cause of death for 15.1%. In the immediate ART group, no AIDS-related causes of death were documented. The most common non-AIDS cause was cardiovascular disease (36.8%). Among those in the delayed ART group, 41.4% died from AIDS-related causes, whereas 55.1% died from non-AIDS-related causes. In the no ART group, a majority of deaths were documented as having non-AIDS-related causes (77.6%), the most frequent of which were other diseases (13.9%), respiratory disease (13.1%), and non-disease-related deaths/accidents (12.9%).

Factors Associated With Death

Factors associated with death within 1 year are presented in Table 2. Higher risk of death was associated with older age (30–49 years: adjusted HR, 2.03, $P < .001$; ≥50 years: adjusted HR, 6.10, $P < .001$), being male (adjusted HR, 1.90, $P < .001$), having only a junior middle school education or less (adjusted HR, 1.85, $P < .001$), and having been infected via heterosexual contact (adjusted HR, 4.16, $P < .001$) or injection drug use (adjusted HR, 5.07, $P < .001$). As far as the timing of ART initiation, immediate ART (initiating within 30 days of diagnosis) provided the

Table 2. Cox Proportional Hazards Regression Models for Mortality Rates and Associated Risk Factors

Characteristic	Entire Study Cohort, No. (%)	Deaths, No. (%)	Observed Time[a], PY	Mortality Rate per 100 PY	Unadjusted HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value
Total	34 581 (100.0)	790 (100.0)	34 188	2.31				
Age, y								
18–29	14 771 (42.7)	122 (15.4)	14 718	0.83	1.00		1.00	
30–49	14 976 (43.3)	334 (42.3)	14 809	2.26	2.72 (2.21–3.35)	<.001	2.03 (1.64–2.52)	<.001
≥50	4834 (14.0)	334 (42.3)	4661	7.17	8.65 (7.03–10.64)	<.001	6.10 (4.87–7.64)	<.001
Sex								
Male	25 927 (75.0)	629 (79.6)	25 616	2.46	1.31 (1.10–1.56)	.002	1.90 (1.59–2.27)	<.001
Female	8654 (25.0)	161 (20.4)	8573	1.88	1.00		1.00	
Ethnicity								
Han	24 969 (72.2)	543 (68.7)	24 692	2.20	1.00		1.00	
Other	9612 (27.8)	247 (31.3)	9497	2.60	1.18 (1.02–1.38)	.03	1.09 (.93–1.28)	.30
Education level								
Junior middle school or less	22 039 (63.7)	688 (87.1)	21 691	3.17	3.89 (3.16–4.78)	<.001	1.85 (1.48–2.31)	<.001
Senior middle school or higher	12 542 (36.3)	102 (12.9)	12 498	0.82	1.00		1.00	
Marital status								
Single, divorced, or widowed	21 019 (60.8)	411 (52.0)	20 814	1.97	1.00		1.00	
Married or cohabitating	13 562 (39.2)	379 (48.0)	13 375	2.83	1.44 (1.25–1.65)	<.001	0.88 (.76–1.02)	.928
Transmission route								
Heterosexual contact	20 713 (59.9)	623 (78.9)	20 394	3.05	7.04 (5.19–9.56)	<.001	4.16 (2.99–5.77)	<.001
Male-to-male sexual contact	10 167 (29.4)	44 (5.6)	10 145	0.43	1.00		1.00	
Injection drug use	3701 (10.7)	123 (15.6)	3649	3.37	7.77 (5.51–10.97)	<.001	5.07 (3.49–7.35)	<.001
ART status[b]								
Immediate ART	1838 (5.3)	19 (2.4)	1828	1.04	0.44 (.28–.69)	<.001	0.37 (.23–.58)	<.001
Delayed ART	5640 (16.3)	58 (7.3)	2583	2.25	0.80 (.61–1.05)	.11	0.74 (.57–.98)	.04
No ART	27 103 (78.4)	713 (90.3)	29 778	2.39	1.00		1.00	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; PY, person-years.

[a]Observed time, in PY, was calculated as beginning on the date of first CD4 test, and ending at 1 year or on the date of death, whichever came first.

[b]ART was treated as the time-dependent variable; immediate ART means ART was initiated within 30 days of confirmed human immunodeficiency virus (HIV) diagnosis; delayed ART means ART was initiated >30 days after diagnosis, but within 1 year; no ART means that ART was never initiated in the 1 year after HIV diagnosis.

strongest protection against death (adjusted HR, 0.37, $P < .001$), while delayed ART (initiating after 30 days of diagnosis, but within 1 year) provided more modest protection (adjusted HR, 0.74, $P = .040$) relative to not receiving ART within the first year.

DISCUSSION

Our results demonstrate that PLWH with a CD4 count >500 cells/μL who initiated ART within 30 days of diagnosis (immediate ART group) experienced a 63% decrease in mortality. Additional risk factors for mortality in this study were older age, being male, having a lesser education, and becoming infected via injection drug use or heterosexual contact. A majority of deaths observed were attributed to non-AIDS-related complications. Our results confirm those from the recent START (strategic timing of antiretroviral treatment) and TEMPRANO (early antiretroviral treatment and/or early isoniazid prophylaxis against tuberculosis in HIV-infected adults – ANRS 12136 TEMPRANO) studies [12, 15], and further indicate that these results are also generalizable to China.

The push for earlier ART initiation has recently been formalized through policy recommendations [16]. Arguments to delay ART initiation based on the use of a CD4 cell count threshold include concerns about drug resistance, side effects, resource allocation, and adherence [24–29]. However, research studies have definitively concluded that the potential clinical and public health benefits of immediate ART initiation far outweigh the risks. Our results highlight the urgency of immediate ART initiation among PLWH with high CD4 cell counts.

HIV-infected, ART-naive patients with high CD4 cell counts still experience elevated mortality compared with the general population [30, 31]. Non-AIDS events remain common among this group [32, 33], and non-AIDS-related mortality can exceed AIDS-related mortality [34]. In settings outside of China, a high proportion of non-AIDS mortality has been attributed to illicit drug use, suicide, unintentional injury, and violence [35, 36]. A cohort study of ART-naive PLWH with CD4 count >350 cells/μL in Europe and North America found that only 14.6%

Table 3. Causes of Death During Follow-up

Cause of Death	Entire Study Cohort	ART Timing After Confirmed HIV Diagnosis		
		Immediate ART (≤30 d)	Delayed ART (>30 d)	No ART (>1 y)
Total	790 (100.0)	19 (100.0)	58 (100.0)	713 (100.0)
AIDS-related	119 (15.1)	0 (0.0)	24 (41.4)	95 (13.3)
AIDS-defining cancer	10 (1.3)		1 (1.7)	9 (1.3)
CNS infection	3 (0.4)		1 (1.7)	2 (0.3)
Tuberculosis	15 (1.9)		2 (3.5)	13 (1.8)
Cryptococcal meningitis	4 (0.5)		1 (1.7)	3 (0.4)
Herpes virus infection	4 (0.5)			4 (0.6)
Wasting syndrome	6 (0.8)		2 (3.5)	4 (0.6)
Candidiasis	5 (0.6)		2 (3.5)	3 (0.4)
Recurrent pneumonia	5 (0.6)		1 (1.7)	4 (0.6)
Pneumocystis pneumonia	14 (1.8)		3 (5.2)	11 (1.5)
Cryptosporidiosis	2 (0.3)		1 (1.7)	1 (0.1)
Other infections	12 (1.5)			12 (1.6)
Other	39 (4.9)		10 (17.2)	29 (4.1)
Non-AIDS-related	603 (76.3)	18 (94.7)	32 (55.1)	553 (77.6)
Non-AIDS-defining cancer	80 (10.1)		4 (6.9)	76 (10.7)
Cardiovascular disease	94 (11.9)	7 (36.8)	6 (10.3)	81 (11.4)
Overdose of illicit drugs	45 (5.7)	1 (5.3)	1 (1.7)	43 (6.0)
Suicide	35 (4.4)	2 (10.5)	2 (3.5)	31 (4.3)
Hepatitis B or C virus	12 (1.5)	1 (5.3)	1 (1.7)	10 (1.4)
Respiratory disease	98 (12.4)	3 (15.8)	2 (3.5)	93 (13.1)
Metabolic disease	10 (1.3)	2 (10.5)	2 (3.5)	6 (0.8)
Gastrointestinal disease	22 (2.8)		1 (1.7)	21 (3.0)
Medicine-related events	1 (0.1)			1 (0.1)
Other diseases	107 (13.6)	2 (10.5)	6 (10.3)	99 (13.9)
Non-disease-related death/accident	99 (12.5)		7 (12.0)	92 (12.9)
Unknown	68 (8.6)	1 (5.3)	2 (3.5)	65 (9.1)
Unclassified	66 (8.3)	1 (5.3)	2 (3.5)	63 (8.8)
Missing	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.3)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; CNS, central nervous system; HIV, human immunodeficiency virus.

of deaths were categorized as AIDS-related, whereas 44.9% were categorized as non-AIDS-related (40.6% of deaths in the study were due to unknown causes) [30]. In our study, 94.7% of deaths in the immediate ART group, 55.1% in the delayed ART group, and 77.6% in the no ART group were classified as non-AIDS-related deaths [34]. Consistent with other studies, the most common causes of death observed were cardiovascular disease, liver disease, non-AIDS-defining malignancies, overdose, suicide, and accidental deaths [33, 35–38].

In addition to the direct benefit of ART for survival, it is also likely that regular follow-up and comprehensive care services associated with ART use contributed to the decreased mortality observed. After ART initiation, patients entered into the stable care system and received multidisciplinary services including regular medical visits as well as psychosocial support [39, 40]. ART clinics provided chronic disease management and cancer and cardiovascular disease screening, which may have contributed to the improvement in health outcomes observed [41–43]. Our study design did not allow us to discriminate the relative contribution of ART vs close medical monitoring. However, the fact that a similar benefit in clinical outcomes was observed in randomized clinical trials [12, 15], where clinical follow-up was standardized between study arms, suggests that our conclusion regarding the benefit of ART at high CD4 cell counts is valid.

Other risk factors for mortality in this study included older age, being male, acquiring HIV through injection drug use or heterosexual transmission, and low educational attainment. In China, HIV incidence has been increasing among older males, particularly in rural areas, who are mainly infected through engaging in commercial sex [44]. Older HIV-infected individuals are more likely to present with comorbidities that increase their risk of death [45]. Mortality was highest among injection drug users, which is related to a variety of factors including delayed ART initiation, poor ART adherence, concomitant drug use, and comorbidities such as depression and hepatitis C virus infection [46].

In contrast to other studies that have examined ART initiation at high CD4 counts [14], an important strength of this study was that all participants who initiated ART in our cohort did so when their CD4 count was >500 cells/μL. Nevertheless, our study had several limitations. As with any observational study, our data should be interpreted with caution, as participants may have had individual circumstances that could have influenced their treatment initiation decisions, including medical comorbidities. Also, because we used routine care data, we did not have access to some potentially informative variables, such as viral load results, details on complications, and, in some cases, causes of death. Moreover, the delayed ART group and no ART group were subject to a survival bias, as the immediate ART group always included persons who lived long enough to initiate ART. To partially avoid this bias, we treated ART as a time-dependent variable. Finally, as the start of follow-up time was date of CD4 test, and those in the delayed ART group tended to have longer median durations between CD4 testing and ART initiation, the shorter time on ART during follow-up may have contributed to poorer outcomes in this group.

CONCLUSIONS

Our results demonstrate that immediate ART initiation within 30 days among PLWH with CD4 counts >500 cells/μL is associated with a 63% reduction in overall mortality. Our results highlight the significant negative impact of delays in ART initiation in a real-world setting in China. Our findings are consistent with the results of recent randomized controlled trials and demonstrate that these results are generalizable. Furthermore, our results support the urgent need to increase the number of PLWH identified early and started on effective, long-term

ART immediately [13, 47], as predicated by the United Nations 90-90-90 targets [38, 48, 49].

Notes

Author contributions. Y. Z. and Z. W. designed the study. Y. Z. performed the statistical analysis. Y. Z., Z. W., J. M. M., C. X. S., R. B., J. S. G. M., and R. D. interpreted the results and developed the initial draft of manuscript. All authors contributed to manuscript revisions and approved the final version for publication. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

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