

Research Article

Gaps in the Continuum of HIV Care: Long Pretreatment Waiting Time between HIV Diagnosis and Antiretroviral Therapy Initiation Leads to Poor Treatment Adherence and Outcomes

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Background. Criteria for antiretroviral treatment (ART) were adjusted to enable early HIV treatment for people living HIV/AIDS (PLHIV) in China in recent years. This study aims to determine how pretreatment waiting time after HIV confirmation affects subsequent adherence and outcomes over the course of treatment. **Methods.** A retrospective observational cohort study was conducted using treatment data from PLHIV in Yuxi, China, between January 2004 and December 2015. **Results.** Of 1,663 participants, 348 were delayed testers and mostly initiated treatment within 28 days. In comparison, 1,315 were nondelayed testers and the median pretreatment waiting time was 599 days, but it significantly declined over the study period. Pretreatment CD4 T-cell count drop (every 100 cells/mm³) contributed slowly in CD4 recovery after treatment initiation (8% less, $P < 0.01$) and increased the risk of poor treatment adherence by 15% (ARR = 1.15, 1.08–1.25). Every 100 days of extensive pretreatment waiting time increased rates of loss to follow-up by 20% (ARR = 1.20, 1.07–1.29) and mortality rate by 11% (ARR = 1.11, 1.06–1.21), based on multivariable Cox regression. **Conclusion.** Long pretreatment waiting time in PLHIV can lead to higher risk of poor treatment adherence and HIV-related mortality. Current treatment guidelines should be updated to provide ART promptly.

1. Background

To date, antiretroviral treatment (ART) is the most effective way to reduce HIV-related mortality among people living with HIV (PLHIV) and prevent further transmission of the virus [1, 2]. In 2014, the Joint United Nations Programme on HIV and AIDS (UNAIDS) announced an ambitious “90-90-90” goal, in which, by 2020, 90% of HIV-infected individuals would be diagnosed, 90% would receive ART treatment after

diagnosis, and 90% would achieve viral suppression as a result of effective treatment [3, 4]. Treatment outcomes of ART may be influenced by multiple factors, but the key one is the timeliness of treatment initiation [5, 6], which relies on the early diagnosis of the infection [7, 8]. In 2015, WHO announced its latest treatment guidelines which recommend PLHIV to initiate ART regardless of CD4 level soonest after diagnosis [9]. Developed countries in Europe have already implemented the WHO recommendations [10]. US panels

also recommended that all individuals with detectable viral loads should receive ART regardless of their CD4+ T-cell counts in 2016 [11]. There is an increasing consensus that ART should be provided to PLHIV as soon as they are diagnosed if resources are available.

The Chinese treatment threshold is synchronously updated with WHO recommendations. In 2008, treatment threshold was improved from the 2002 level of 200 cells/mm³ to 350 cells/mm³ [12]. In 2014, the threshold was further increased 500 cells/mm³ [13]. Currently, the Chinese National Centre for Disease Control and Prevention (CDC) is considering removing CD4 requirements completely to allow patients to initiate treatment at any time after HIV diagnosis. However, given that most PLHIV were diagnosed with a low CD4+ T-cell count [14], removing the treatment threshold may not have a real impact on improving ART coverage. Besides, the treatment resources were not distributed evenly in China, in resource-limited areas, treatment has to be prioritised to PLHIV diagnosed with a low CD4 count [15]. By far no strong evidence in China proves ART with removing CD4 threshold is effective to help the various population in China. Thus, despite updates in treatment guidelines nowadays, many PLHIV patients still experience long waiting time before their CD4+ T-cell counts fall below the threshold level to be qualified for treatment. It is unclear whether these patients, despite linked to HIV care, can benefit from ART to the full extent if they delay their treatment.

Yuxi, with 2.3 million residents, is the third-largest city in Yunnan province in Southwest China. The city is located 100 kilometres south of Kunming, the capital of Yunnan Prefecture, and approximately 300 kilometres north of Vietnam. Its proximity to the traditional drug trafficking route attributes to a size population of injecting drug users (IDUs) [16], resulting in Yuxi having one of the highest HIV rates in China [17]. ART was substantially scaled up in Yuxi in 2004 and provided to over 2,741 PLHIV since then. This study aimed to investigate whether the time elapsed between HIV diagnosis and ART initiation and the variation in CD4+ T-cell level prior to treatment initiation may have strong implications to the subsequent treatment effectiveness.

2. Methods

2.1. Data Sources. Data was extracted retrospectively from the treatment and epidemiology databases of the Yuxi CDC. Both databases were maintained according to the requirements of China CDC. The treatment database contained information on all PLHIV who began ART treatment in Yuxi between 2004 and 2015. The epidemiology database contains the results of CD4+ T-cell counts tests taken before ART treatment of patients diagnosed in Yuxi between 1996 and 2015. For the study, each patient's name and another identifiable information in the databases were replaced by a unique code, which was used to link the information in both databases about each subject, enabling the study to collect data on each patient from both before and after ART initiation. The study was approved by Monash University Research Ethics Committee (Project number 0651).

2.2. Inclusion Criteria. The study included participants within the study jurisdiction who were 18 years old or older at the time of ART initiation during the study period, which was between 1 January 2004 and 31 December 2015. The study excluded patients whose data could only be found in one of the epidemiology and treatment databases or who died from any causes other than an HIV-related one (like accidents, suicide, and others) during the study period. Matching the two databases ensures the completeness of indicators for subsequent analysis.

2.3. Baseline Variables. The study collected patients' demographic characteristics at ART initiation, including age, gender, body mass index (BMI), and marital status. Data regarding the date of HIV diagnosis, HIV transmission route, initial CD4 tests, and ART initiation (including CD4+ T-cell counts, WHO HIV clinical stage, and complications) were collected from each patient's initial clinical assessment. Included patients were categorised into two groups by their detention status: (1) delayed testers and (2) nondelayed testers. According to the international criteria, delayed testers were defined as those with CD4+ T-cell counts < 200 cells/mm³, who were categorised as being in the WHO clinical stage IV, within 360 days after confirmation of HIV-positive status [18]. After categorising the patients as delayed or nondelayed, the two groups were compared for the following: demographic characteristics, baseline variables, and three important indicators. Specifically, these indicators include the days between HIV diagnosis and ART initiation, which was used to demonstrate how long a patient should wait for treatment according to the previous criteria and the elapsed time from HIV diagnosis to CD4 testing, which represents how quickly a patients were connected to HIV care; in the nondelayed group, the various values and rates of decrease CD4+ T-cell counts were recorded as an independent variable, which has reflected the function of immune system of patients before ART. The declined value was stratified into five groups by every 100 cells/mm³ for the purpose of analyzing the relationship between the pretreatment CD4+ T-cell counts decline difference and treatment outcomes (Figure 1).

2.4. Outcome Variables. There are three outcome variables in the study: (1) immunological response (CD4+ T-cell count increase) during the first 6–12 months after ART initiation, (2) subsequent HIV-related mortality, and (3) loss to follow-up (Figure 1).

2.5. Statistical Analyses. The study conducted both descriptive and inferential statistical analyses. Median and interquartile ranges (IQR) were used to summarise numerical variables, whereas frequency times and percentages were used to summarise categorical variables. The temporal trend of the duration of diagnosis and treatment and the duration between diagnosis and first CD4+ T-cell testing was calculated by linear trend test. A linear trend test was also used to investigate the CD4+ T-cell counts variation value associated with immunological response in the first 6–12

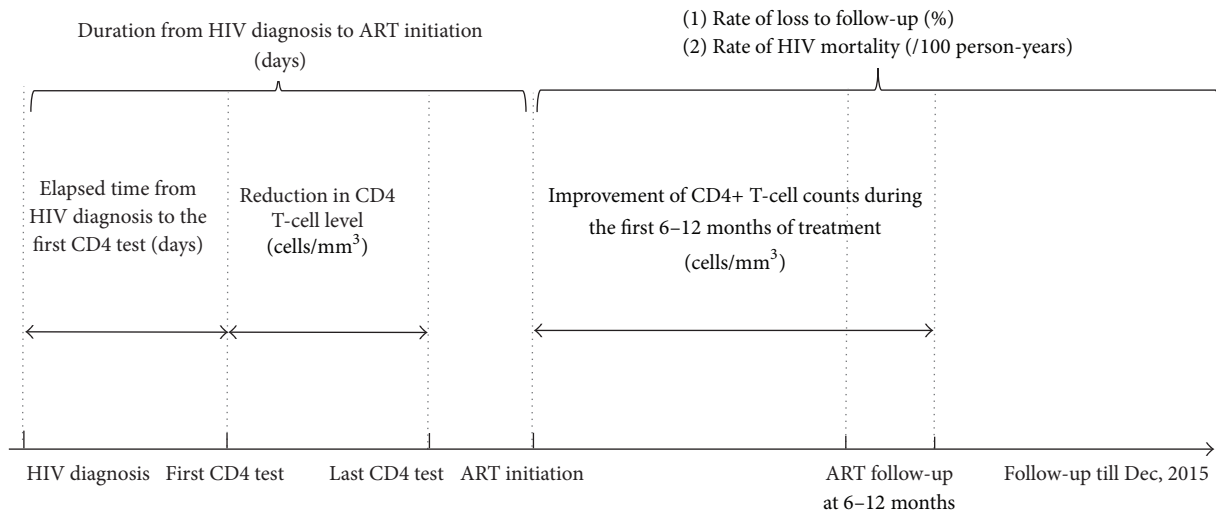


FIGURE 1: Illustration of key indicators used in this study.

months of treatment. Adjusted relative risks (ARRs) accompanied by 95% confidence intervals (CIs) were calculated. A multivariable Cox regression was used to identify key factors related to mortality and adherence rate. The mortality rate was calculated as the number of recorded deaths divided by the total number of person-years (PYs) from the initiation of treatment to the end of follow-up. The rate of loss to follow-up was calculated as the number of participants with recorded ART discontinuation divided by the total number of PYs in the same period. Variables with a P value < 0.2 in the univariate analysis were included in the multivariate analyses. Collinearity was checked by evaluating the impact factors of all the indicator variables in the multivariate analyses. Data management and analysis were conducted using Statistical Analysis System 9.4, with P values set at < 0.05 throughout. Missing data were included as “unknown.”

3. Results

3.1. Baseline of Participant Characteristics. A total of 1,953 PLHIV adults enrolled in this study over the period from January 2004 to December 2015. We excluded 155 patients who were only in the epidemiology database, 109 patients were only in the treatment database, and 26 patients died of non-HIV-related causes (19 from nondelayed testers and 7 from delayed testers). The remaining 1,663 PLHIV were finally included. Among them, 348 (20.9%) were delayed testers while 1,315 (79.1%) were nondelayed testers. The median age of participants was 36 years (IQR 30–45), and the median body measure index (BMI) was 21.3 kg/m² (IQR 19.3–23.1). Delayed testers were significantly elder (42 years [34–50] versus 35 years [30–43], $P < 0.01$) and with lower BMI (19.1 kg/m² [17.4–20.8] versus 21.4 kg/m² [19.5–23.2], $P < 0.01$) than nondelayed population. People who acquired HIV by sharing of injection equipment (39, 11.1%) have a lower proportion among nondelayed testers (313, 23.8%) than

delayed testers ($P < 0.01$). Among PLHIV with known hepatitis infection status, patients in the nondelayed group have a higher HCV coinfection rate than the delayed group (225, 24.7% versus 28, 11.7%, $P < 0.05$), while the HBV coinfection prevalence did not differ between the two groups (64, 6.3% versus 18, 6.8%, $P = 0.76$) (Table 1). At the diagnosed stage, HCV prevalence in the nondelayed group was 20.2% (88/435) and 12.4% (21/169) in delayed testers. HBV prevalence in two groups was 5.7% (25/435) and 5.9% (10/169), respectively.

3.2. Pretreatment Waiting Time and Disease Progression. It was found that nondelayed testers had to wait much longer to receive ART after HIV diagnosis than the delayed testers (599, [interquartile range, IQR = 54–1740] versus 28 [15–56] days) although the waiting time from diagnosis to the first CD4 test was similar (13 [7–22] days versus 16 [7–56.5] days, resp.). However, temporally, waiting time for nondelayed testers has significantly declined during 2004–2015. The days between HIV infection confirmation and treatment declined from 1706 (IQR: 507–3,123) in 2004–2006 to 762 days IQR (243–1,611) in 2007–2009 then 588 days IQR (69–1,548) in 2010–2012 and 447 days IQR (37–1,639) in 2013–2015 (linear trend test, $P < 0.05$), respectively. Similarly, the elapsed time from diagnosis to first CD4 test, which represented the time taken to link to HIV care, declined from 99 days (56–117) to 11 days (4–23) over the same period (Figures 2(a) and 2(b)).

3.3. Predictors of Treatment Effects and Adherence. The pretreatment variation of the CD4 level and waiting time determined long-term ART outcomes. We found that long-term ART effects and pretreatment drop difference (every 100 cells/mm³) were associated with 8% reduction in CD4 recovery after treatment initiation (linear trend test, $P < 0.01$) (Figure 3). Of 1,663 participants, 169 patients died due to HIV-related diseases over the treatment follow-up. As for

TABLE 1: Key demographic characteristics and hepatitis coinfection prevalence rates of participants in Yuxi, China, stratified by delayed testers and nondelayed testers.

	Total	Delayed testers	Nondelayed testers	P value
Demographic characteristics	1663 (100%)	348 (20.9%)	1315 (79.1%)	
Gender				0.02
Female	661 (39.7%)	120 (18.2%)	541 (81.8%)	
Male	1002 (60.3%)	228 (22.8%)	774 (77.2%)	
Age (IQR)	36 (30–45)	42 (34–50)	35 (30–43)	<0.01
BMI (IQR)	21.3 (19.3–23.1)	19.1 (17.4–20.8)	21.4 (19.5–23.2)	<0.01
Marriage status				0.04
Married	1156 (69.5%)	263 (22.8%)	893 (77.2%)	
Single	261 (15.7%)	41 (15.7%)	220 (84.3%)	
Divorced	181 (10.9%)	36 (19.9%)	145 (80.1%)	
Widowed	62 (3.7%)	8 (12.9%)	54 (87.1%)	
Unknown	3 (0.2%)	0 (0%)	3 (100%)	
Transmission route				<0.01
Heterosexuals	1158 (69.6%)	265 (22.9%)	893 (77.1%)	
IDU	352 (21.2%)	39 (11.1%)	313 (88.9%)	
Homosexuals	46 (2.8%)	9 (19.6%)	37 (80.4%)	
FPD	9 (0.5%)	2 (22.2%)	7 (77.8%)	
Unknown	98 (5.9%)	33 (33.7%)	65 (66.3%)	
ART initiation year				0.04
2004–2006	19 (1.1%)	7 (36.8%)	12 (63.2%)	
2007–2009	218 (13.1%)	53 (24.3%)	165 (75.7%)	
2010–2012	602 (36.2%)	139 (23.1%)	463 (76.9%)	
2013–2015	796 (47.9%)	149 (18.7%)	647 (81.3%)	
Unknown	28 (1.7%)	0 (0%)	28 (100%)	
CD4 counts at ART initiation				<0.01
0–200	513 (30.8%)	339 (66.1%)	174 (33.9%)	
200–350	641 (38.5%)	8 (0.4%)	633 (96.4%)	
350–500	258 (15.5%)	1 (0.1%)	257 (99.9%)	
>500	251 (15.1%)	0 (0%)	251 (100%)	
Hepatitis coinfection				
HCV coinfection				<0.001
Positive	253 (15.2%)	28 (11.7%)	225 (24.7%)	
Negative	897 (53.9%)	212 (88.3%)	685 (76.3%)	
HBV coinfection				0.76
Positive	82 (4.9%)	18 (6.8%)	64 (6.3%)	
Negative	1193 (71.7%)	245 (93.2%)	948 (93.7%)	

elevating mortality, every 100 days of extensive pretreatment waiting time increased HIV-mortality rate by 11% during the following course of ART (ARR = 1.11, 1.06–1.21). However, pretreatment CD4 decline did not affect subsequent mortality. Other independently associated factors of mortality included being older (ARR = 1.07, 1.04–1.09), initiated ART in 2007–2009 (ARR = 2.05, 1.26–4.35 versus patients started treatment in 2013–2015), and HIV infected by drug injection (ARR = 2.88, 1.34–6.17) (Table 2).

Among all the alive patients, 68 (4.6%) have discontinued treatment during the study period. Based on the multivariable Cox regression model, every drop of 100 cells/mm³ in CD4 level before treatment could increase the risk of nonadherence by 15% (ARR = 1.15, 1.08–1.25). Every 100 days of

extensive pretreatment waiting time increased rates of loss to follow-up by 20% (ARR = 1.20, 1.07–1.29). Delayed testers (ARR = 1.49, 1.30–1.72) and aging (ARR = 1.07, 1.04–1.09) were associated with elevated risks of loss to follow-up as well. In terms of transmission route, IDU has suboptimal performance compared with heterosexuals. The risk of loss to follow-up was increased to 1.53-fold 95% CI (1.11–2.11) among IDU (Table 2).

4. Discussion

This study demonstrated a significant declining trend in the number of delayed testers, the duration of HIV diagnosis and treatment, and the duration between diagnosis and the

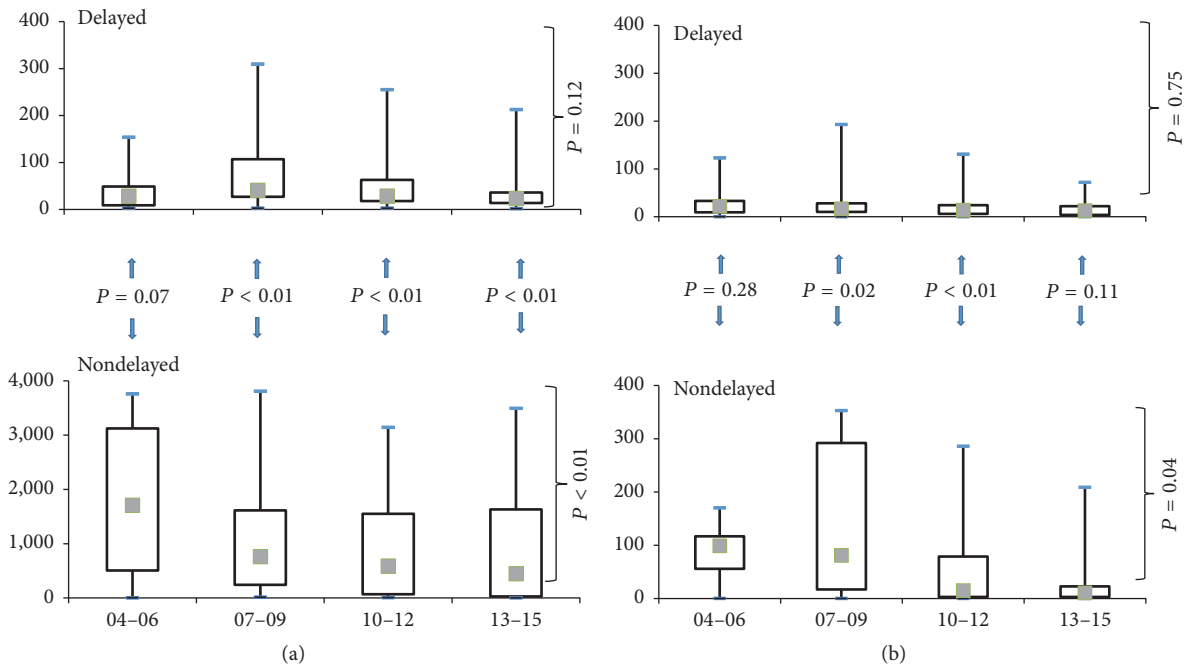


FIGURE 2: (a) Days between HIV-positive and ART initiation (delayed and nondelayed). (b) Days between HIV-positive and first CD4 testing date (delayed and nondelayed).

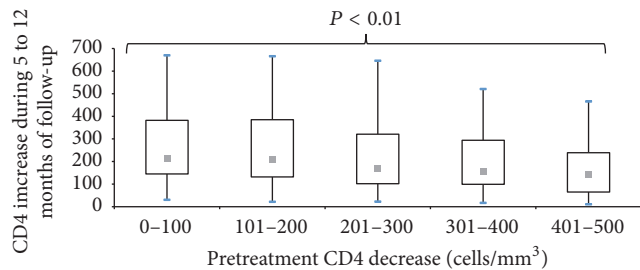


FIGURE 3: The association between CD4+ T-cell counts decrease value before ART initiation and CD4+ T-cell counts increase during first six to twelve months after treatment initiation.

first CD4 test date, consistent with the rising CD4 treatment threshold in the treatment guidelines during the study period. The pretreatment elapsed time in the delayed-tester group was remained unchanged in the same period, indicating HIV care has been provided promptly to PLHIV with very low CD4 T-cell counts or those clinically viable. Pretreatment waiting time and CD4 decline are important determining factors of subsequent ART adherence, HIV-related mortality, and immune response.

The duration between HIV diagnosis and first CD4+ T-cell counts testing is similar between delayed testers and nondelayed testers. This suggests that most PLHIV enter HIV care quickly within two weeks of diagnosis. Thus, it illustrates that even if nondelayed patients expect to start antiretroviral therapy as soon as the delayed testers, the Chinese treatment program may still be able to cover them sufficiently. In contrast, the duration of HIV diagnosis to first CD4+ T-cell

counts test in the nondelayed testing group was shortened gradually, which echoes the enactment of the “Four Frees and One Care” policy in China in 2004 and the scale-up of ART program that improves the linkage of diagnosed patients to care [19].

In contrast to the delayed testing group, the majority of the nondelayed testing group have to wait over a year to initiate ART according the treatment guidelines’ standards. Although the treatment threshold has gradually increased over the years (200 cells/mm³ in 2002, 350 in 2008, and 500 in 2014) [20], patients in the nondelayed group often have to wait significantly longer than the delayed testing group to be qualified for treatment. Our finding indicates that the wait leads to the potentially higher risk of HIV-related mortality subsequently, due to two main weaknesses. First, patients may continue their risk behavioural pattern in the absence of suitable intervention after diagnosis, which accelerate HIV disease progression or being coinfectd by other blood-borne and sexually transmitted infections. Previous studies confirmed that ART reduces their high-risk behaviour as a clinical health care can target and monitor patients in a routine manner [21, 22]. Given that patient in the nondelayed group has a higher proportion of IDUs (23%) than that of the delayed group (11%), HCV infection is therefore likely more common in this group at ART initiation. It is well known that HIV coinfection would complicate the treatment and increased treatment failure risk leading to high mortality [23–25]. Furthermore, during the pretreatment period, HIV-positive patients with high CD4 counts may regard themselves as the health and neglect medical advice [26]. In contrast, patients who have received correct knowledge about ART and would initiate therapy earlier after diagnosis would

TABLE 2: Predictors of loss to follow-up and HIV-related mortality over the whole study period among eligible participants in the ART observational database of the Yuxi District.

	Loss to follow-up		Mortality	
	Cases/participant, person-years	ARR, <i>P</i> value	Cases/participant, person-years	ARR, <i>P</i> value
Delayed status				
Nondelayed testers	56/1212, 3869	Ref.	103/1315, 3995	Ref.
Delayed testers	12/282, 1129	1.49 (1.30–1.72), <0.01*	66/348, 1243	1.43 (0.68–2.26), 0.48
Gender				
Female	18/623, 1831	Ref.	38/661, 2038	Ref.
Male	50/871, 3167	1.06 (0.95–1.19), 0.29	131/1002, 3200	1.44 (0.68–3.06), 0.34
Age	68/1494, 4998	1.01 (1.00–1.01), <0.01*	169/1663, 5238	1.07 (1.04–1.09), <0.01*
Transmission route				
Heterosexuals	37/1073, 3226	Ref.	85/1158, 3341	Ref.
IDU	27/282, 1294	1.53 (1.11–2.11), <0.01*	70/352, 1368	2.88 (1.34–6.17), <0.01*
FPD	0/9, 24	—	0/9, 24	0
MSM	0/44, 99	—	2/46, 100	0.54 (0.07–4.40), 0.57
Unknown	4/86, 355	1.23 (0.83–1.47), 0.19	12/98, 405	2.11 (0.87–2.81), 0.33
Pretreatment waiting time (every 100 days) in nondelayed	56/1212, 3869	1.20 (1.07–1.29), <0.01*	103/1315, 3995	1.11 (1.06–1.21), <0.01*
Pretreatment CD4 decline (every 100 cells/mm ³) in nondelayed	56/1212, 3869	1.15 (1.08–1.25), <0.01*	103/1315, 3995	1.10 (0.96–1.16), 0.78
ART initiation year				
2013–2015	32/754, 1590	Ref.	42/796, 1636	Ref.
2010–2012	22/521, 1936	0.80 (0.67–1.65), 0.53	69/590, 1981	1.32 (0.61–2.90), 0.48
2007–2009	14/169, 1089	0.69 (0.38–1.68), 0.54	49/218, 1205	2.05 (1.26–4.35), 0.01*
2004–2006	0/15, 166	—	4/19, 190	0.92 (0.76–8.13), 0.35
Unknown	0/23, 217	—	5/28, 226	0.98 (0.78–6.25), 0.31

*Result is significant at the 0.05 level of *P* value.

be more adaptable to adhere to it [27]. This hypothesis is consistent with our results that follow-up status of the long waiting treatment population is not ideal. Since adherence rate is a key factor to ensure the treatment effects from lots of previous studies [28, 29], patients who wait for a long time have higher death rate accordingly. The reduction in waiting time and the number of delayed testers may attribute to the scale-up of the national HIV testing program, free treatment policy, and improved treatment criteria [14, 30].

Pretreatment CD4 drop is a precursor of ART treatment outcomes and is associated with a much slower recovery of CD4 level at 6–12 months into treatment. Previous studies have reported that patients with CD4+ T-cell counts less than 200 cells/mm³ have impaired immunological recovery compared with those start ART while CD4+ T-cell counts

above 350 cells/mm³ [31, 32]. Our finding also indicated that patients who have a greater CD4 drop may be more likely to discontinue treatment follow-up in the long term. This shows that patients who overlooked own health in waiting duration would be prone to disregard the medical care as well. In clinical settings, doctors can suggest patients with slow CD4 increase test for drug resistance [33]. In the presence of drug resistance, clinical doctors should change the regimen for the patients. Otherwise, doctors should encourage patients to continue treatment to ensure CD4 counts stable, which is still helpful for immune reconstitution and rule out other causes of weak immunological responses [34, 35].

Notably, screening of HIV among drug users has reached a high coverage in Yuxi County, but the following HIV treatment comes too late, indicating a weak link in the cascade

of HIV treatment. This is reflected by the fact that IDU constitutes a smaller proportion in the delayed group than the nondelayed participants, but with a higher mortality and loss-to-follow-up rate during the treatment than heterosexuals. As mentioned in the background, the high-risk population in Yuxi mainly concentrate in IDU. In this situation, local health institute has conducted appropriate prevention for testing to curb the transmission among this group [36, 37]. However, the later follow-up monitoring did not treat IDU as a priority after diagnosis resulting in part of drug users initiate ART late and also a lack of the recommendations from the treatment guidelines was another reason for IDU to start ART late. Thus, specific support is still necessary for the IDU who have HIV-positive confirmed and started ART.

Other independent factors are also associated with mortality or loss-to-follow-up rate. Being enrolled into ART in 2007–2009 led to higher death rate than people started in 2013–2015. It may be because the China-free ART program adopted the optimal first-line ART regimen Tenofovir Disoproxil Fumarate (TDF) instead of Stavudine (d4T) since 2009 [38], and the ART treatment threshold was increased from $CD4 \leq 200$ cells/mm³ in 2003 to ≤ 350 cells/mm³ in 2008 also helps to increase the treatment effects [39]. Elder people have higher mortality and loss-to-follow-up rate; this situation is common in the developing countries [40, 41]. As senescence is the nature that human body metabolizes, the function of each organ including immune system has declined with aging which would speed up disease progress.

Several limitations should be noted in this study. First, the patient's health situation of the first CD4+ T-cell test is not collected; the counts would be affected by their infection period or coinfection status. Second, the majority of patients started ART after 2007; this may affect comparability in temporal trend. Third, the study did not capture the detailed information on the reasons when the patients decide to start treatment; this prevents us from excluding patients who delayed the treatment according to the medical suggestions, which leads to selection bias. Fourth, the exact causes of the 26 excluded death cases were not reported by the hospitals to the local CDC. As a result, we cannot independently confirm its relatedness to HIV infection. In this case, HIV-related mortality may be underestimated. Fifth, there was about 7% of entry records not being able to be matched across the two databases. One of the likely reason for this is that these individuals may not have local residence such that they were referred back to their home residence for treatment after diagnosis. Hence, they had no treatment data. However, excluding this small proportion of patients is unlikely to alter the study the conclusions.

5. Conclusion

Long duration before treatment after HIV-infected confirmation negatively affects the ART effects and adherence rate, which is suggested being shortened. The Chinese treatment guidelines should be updated to account for the needs of pretreatment care and special care for patients coinfecting with viral hepatitis. Patients are advised to begin ART when their CD4+ T-cell counts still in the high level. These findings

underline the necessary monitoring for HIV-positive patients before treatment to maximize the ART effects in the long term.

Competing Interests

The authors declare that there are no competing interests.

Authors' Contributions

Lei Zhang, Jun Jing, Liang Chen, and Feng Cheng conceived and designed the study; Shifu Li, Shunxiang Li, Liangmin Gao, Ying Cai, Jincui Fu, and Chunyuan Guo collected the data; Shifu Li cleaned the data; Shu Su and Lei Zhang analyzed the data; Shu Su wrote the paper; Jun Jing, Limin Mao, and Lei Zhang revised the manuscript. All authors approved the final manuscript.

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