Original Article

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Longitudinal impact of compliance with routine CD4 monitoring on all cause deaths among treated people with HIV in China

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SUMMARY Keeping adherence to the continuous and standardized CD4 follow-up monitoring service is of great significance to the control of disease progression and the reduction of avoidable mortality for HIV-infected patients. As non-communicable diseases (NCDs) have become main causes of deaths for people with HIV (PWH) in the era of combination antiretroviral therapy (cART), how and to what extent does adherence to routine CD4 monitoring differentially impact on AIDS-related versus NCDs-related deaths in low- and middle-income countries (LMIC) remains elucidated. A CD4 test index was developed by dividing the actual number of received CD4 tests by the theoretical number of CD4 tests that should have been performed according to national treatment guidelines during the study period, with an index value of 0.8-1.2 reflecting compliance. From 1989 to 2020, 14,571 adults were diagnosed with HIV infection in Dehong Prefecture of Yunnan province in Southwestern China, 6,683 (45.9%) PWH had died with the all-cause mortality of 550.13 per 10,000 person-years, including 3,250 (48.6%) AIDS-related deaths (267.53 per 10,000 person-years). Among patients on cART, the median CD4 test index was 1.0 (IQR 0.6-1.3), and 35.2% had a CD4 test index less than 0.8. Cox proportional hazards regression analysis indicated that PWH with CD4 test index at 0.8-1.2 were at the lowest risk of both AIDS-related (aHR = 0.06; 95%*CI*: 0.05-0.07) and NCDs-related (aHR = 0.13; 95%*CI*: 0.11-0.16) deaths. Adherence to routine CD4 monitoring is critical for reducing both AIDS-related and NCDs-related mortality of PWH. An appropriate (once or twice a year) rather than an unnecessarily higher frequency of routine CD4 testing could be most cost-effective in reducing mortality in LMIC.

Keywords CD4 testing, adherence, mortality, non-communicable disease (NCD), HIV

1. Introduction

Combination antiretroviral therapy (cART) effectively reduces the morbidity and mortality of people with HIV (PWH) and extends their life expectancy to that of the general population (*1*). WHO guidelines proposed in 2015 recommend that HIV-infected patients should immediately initiate cART as soon as they are diagnosed (*2*), as it is related to decreasing morbidity and mortality, reducing HIV transmission (*i.e.*, treatment as prevention, TasP), and reducing loss to HIV healthcare (*3,4*).

Increasing lifespans of PWH and cART may both contribute to development of some non-communicable diseases (NCDs) among PWH. The prevalence of NCDs among PWH is much higher (29-44%) compared to that in the general population (15-25%) (*5*).The co-occurrence of HIV and NCDs remarkably challenges survival and quality of life as well as health care of PWH, especially in low- and middle-income countries (LMIC) (*6,7*). Despite a dramatic decrease in AIDS-related mortality among well-treated PWH, their life expectancy are compromised compared with persons without HIV (*8*). The excess mortality is primarily caused by NCDs, and NCDs had become the leading cause of the increased mortality of PWH globally (*9-11*). These suggest an importance of screening and managing NCDs within health care services provided for PWH.

CD4 testing plays an important role in settings with limited health resources where viral load testing cannot be carried out regularly (*12*). After initiating

cART, keeping adherence to the continuous and standardized CD4 follow-up monitoring service is of great significance to the control of disease progression and reduction of avoidable mortality for HIV-infected patients (*13*). Some recent studies suggest that in the early phase of cART, continuous CD4 monitoring helps identify immunosuppressed patients and detect the risk of progression to AIDS (*14,15*). However, it is noted that HIV-infected patients who are not immunocompromised and well adhere to cART may not benefit from regular CD4 testing (*16*).

Since the National Free Antiretroviral Treatment Program (NFATP) was established in 2003 in China (*17*), AIDS-related deaths among PWH have substantially decreased, particularly as cART has now been scaled up to over 95% of PWH and is available to all newly diagnosed HIV infections regardless of their CD4 counts or immunodeficiency status. However, consistent with other countries, there are emerging observations that PWH in China are at significantly higher risks of NCDs than the general population and are increasingly overtaken by NCDs in both morbidities and mortalities (*18*). Meanwhile, the national guideline for cART and health management of PWH in China has developed to the Fourth Edition, reflecting periodic changes and adjustments in standard clinical practices and treatment for PWH. Accordingly, the agenda of routine CD4 testing after initiating cART for regular care of PWH has also been changing. Before 2012, a CD4 test was performed in the 3rd, 6th, and 12th month in the first year after initiation of cART, and once per 6 months afterwards (1st Edition before 2008 and 2nd Edition during 2008-2012); from 2012 to 2016, a CD4 test was performed once per 6 months after initiation of cART (3rd Edition), and from 2016 to now, a CD4 test was performed at least once a year (4th Edition). Nonetheless, no longitudinal studies have been conducted to comprehensively evaluate the impact of compliance with routine CD4 testing on the health outcomes particularly AIDS-related and NCDs-related deaths among PWH in China.

The objective of this study was to characterize and determine the mortality of AIDS-related deaths and NCDs-related deaths among PWH in Dehong Prefecture of Yunnan province in Southwestern China, which has the longest history of HIV epidemic and most comprehensive anti-HIV campaigns (*19*), and to identify how and to what extent compliance with routine CD4 monitoring has impacted on AIDS-related versus NCDs-related deaths.

2. Materials and Methods

2.1. Study design

This is a retrospective cohort study conducted in Dehong Prefecture. Data were derived from China's HIV/AIDS Comprehensive Response Information Management System (CRIMS), a nationwide real-time reporting system composed of eight subsystems (*20*). Participants gave informed consent to participate in the study. This study was approved by the Institutional Review Board of Fudan University School of Public Health, Shanghai, China (IRB#2018-01-0655).

2.2. Setting and participants

2.2.1. Patients

Patients were eligible for the present study if they were older than 18 years at HIV diagnosis, were local residents of Dehong Prefecture and were not infected through mother-to-child transmission. For all eligible patients, the observational period was from the date of cART initiation (*i.e.*, baseline) through 31 December 2020 or death. Accordingly,14,571 adults diagnosed with HIV in Dehong Prefecture (the lost to follow-up rate was 0.02%) were subject to the analysis.

2.3. Definitions and variables

2.3.1. Definitions

CD4 test index: A CD4 test index reflecting compliance with CD4 testing was developed by dividing the actual number of received CD4 tests by the theoretical number of CD4 tests that should have been performed according to the national guidelines during the study period. The CD4 test index was then categorized into four groups as the following: ≤ 0.3 (severe incompliance), > 0.3 & ≤ 0.8 (medium incompliance), > 0.8 & ≤ 1.2 (compliance) and > 1.2 (over compliance).

AIDS-related deaths: since 2011, Dehong Prefecture Center for Disease Control and Prevention (CDC) has conducted three waves of confirmatory inspections on the causes of deaths among HIV-infected persons who had instantaneous registration of death in the CRIMS. For the present study, the detailed causes of deaths were extracted from the CRIMS and compared with the Coding of Death in HIV (CoDe) protocol to determine AIDS-related deaths. For patients whose causes of deaths were unknown, the deaths were considered to be AIDS-related if they had CD4 count < 200 cells/μL within 6 months before death.

NCDs-related deaths: if a patient died from any of cardiovascular diseases (CVDs), cancers, chronic respiratory diseases, diabetes, mental disorders recently added to the list of major NCDs, and other NCDs-related diseases defined in the International Classification of Diseases, 10th revision (ICD-10), the death was defined as NCDs-related.

2.3.2. Data collection

Information about socio-demographic variables, date of

HIV diagnosis, HIV transmission route, date of cART initiation, baseline and follow-up CD4 cell counts and HIV viral load (VL) of the participants was extracted from CRIMS.

2.4. Statistical analysis

For mortality rate estimation, the date of HIV diagnosis was used as time of entry, and the date of AIDS-related death or the date of NCDs-related death or the end of observation (December 31, 2020) was regarded as the end date. Those who died of non-AIDS-related and non-NCD-related deaths or were lost to follow-up for > 3 months were considered censored, and the date of death or the date of loss to follow-up was used as the end date. Pearson chi-square test was used to compare categorical variables.

For Kaplan-Meier survival curve of the HIV-infected patients who were receiving cART, the date of cART initiation was treated as time of entry, and the date of AIDS-related or NCDs-related death or the end of observation (December 31, 2020) was as the end date. Those who died of non-AIDS-related or non-NCD-related deaths or lost to follow-up for > 3 months were considered censored, and the date of death or the date of loss to follow-up was used as the end date. Tarone-Ware test was used to compare survivals between groups.

Cox proportional hazards regression model was employed to determine the association between CD4 test index and AIDS-related mortality or NCDs-related mortality. In multivariate analysis, sex, ethnicity, transmission route, age at cART initiation, baseline CD4 count, nadir CD4 count, and baseline HIV viral load were considered to be potential confounding variables that were then entered into the multiple regression model for adjustment, based on literature review and univariate analyses in the present study. Multiple imputation procedure was employed to complete the missing values for baseline viral load. All analyses were performed with SAS (version 9.4).

3. Results

3.1. Characteristics of study participants

From 1989 to 2020, 14,571 adults were diagnosed with HIV in Dehong Prefecture, China, contributing 121,479.9 person-years of follow up (Table 1). Among them, 10,700 (73.4%) were males, 6,848 (46.9%) were diagnosed before 31 years old, 5,122 (35.1%) were Dai ethnicity and 6,503 (44.6%) had acquired HIV through injection drug use (IDU). Noticeably, there was a striking increase of diagnosed HIV infections in 2004 due to a mass screening program, and cART was not available until 2004 (Figure 1A). Thus, only 9,606 (65.9%) participants had received cART.

3.2. CD4 test index

Among 9,606 HIV-infected patients with cART, 9,251 (96.3%) had been on cART for more than one year, had pretreatment baseline CD4 test, and had at least one posttreatment CD4 test. Of them, the median CD4 test index was 1.0 (IQR 0.6-1.3), and 35.2% had a CD4 test index less than 0.8, reflecting noncompliance to CD4 testing (Table 2). As shown in Table 2, the CD4 test index was significantly different by sex, age, ethnicity, HIV transmission route, baseline CD4 count, nadir CD4 count, and baseline HIV viral load.

3.3. AIDS-related *vs*. NCDs-related mortality

The annual number of all-cause deaths had been increasing since 1989, reached peak in 2007, and has then been decreasing (Figure 1B). By the end of 2020, 6,683 (45.9%) patients had died, including 3,250 (48.6%) AIDS-related deaths and 1,734 (26.0%) NCDs-related deaths (Table 1). The all-cause mortality was 550.13 per 10,000 person-years, the AIDS-related mortality was 267.53 per 10,000 person-years and the NCDs-related mortality was 142.74 per 10,000 person-years (Table 1). The all-cause mortality, the AIDS-related mortality, and the NCDs-related mortality were all lower in people with cART than those in people without cART, and were different by socio-demographic and HIV infection characteristics (Table 1).

3.4. Association between CD4 test index and mortality

3.4.1. Survival by CD4 test index

The Kaplan-Meier survival curve showed that treated patients with different CD4 test index had significantly different survival probabilities in terms of AIDS-related, NCDs-related as well as all-cause deaths (all *p-values* < 0.05) (Figure 2). Patients with CD4 test index lower than 0.3 had the lowest survival probability after cART, and patients with CD4 test index of 0.8-1.2 had the highest survival probability (Figure 2A for AIDS-related deaths, Figure 2B for NCDs-related deaths, and Figure 2C for all-cause deaths).

3.4.2. Associates of AIDS-related mortality

As shown in Table 3, univariate COX regression analysis indicated that the AIDS-related mortality was significantly associated with sex, age, ethnicity, HIV transmission route, baseline CD4 count, nadir CD4 count, baseline HIV viral load, and CD4 test index. Such associations remained significant in multivariate COX regression analysis adjusting for confounding variables. In particular, compared to patients with CD4 test index less than 0.3, patients with CD4 test index at 0.3-0.8 (aHR = 0.18, 95%*CI*: 0.15-0.22), 0.8-1.2

Table 1. Baseline characteristics of HIV-infected participants

Characteristics	*N* (%)	Person-years of follow up	All-cause Deaths		AIDS-related Deaths		NCDs-related Deaths		Other Deaths	
			N	Mortality (/10,000 person-years)	*N* (%)[a]	Mortality (/10,000 person-years)	*N* (%)[a]	Mortality (/10,000 person-years)	*N* (%)[a]	Mortality (/10,000 person-years)
Total	14,571	121,479.90	6,683	550.13	3,250 (48.6)	267.53	1,734 (26.0)	142.74	1,699 (25.4)	139.86
Gender										
Male	10,700 (73.4)	86,671.93	5,786	667.60	2,723 (47.0)	314.17	1,455 (25.2)	167.87	1,608 (27.8)	185.53
Female	3,871 (26.6)	34,807.92	897	257.70	527 (58.8)	151.40	279 (31.1)	80.15	91 (10.1)	26.14
Age at diagnosis, yr										
< 30	6,848 (46.9)	64,665.93	3,252	502.90	1,521 (46.8)	235.21	698 (21.4)	107.94	1,033 (31.8)	159.74
31-40	4,556 (31.3)	36,866.75	2,080	564.20	1,057 (50.8)	286.71	536 (25.8)	145.39	487 (23.4)	132.10
41 -50	1,977 (13.6)	13,403.74	806	601.32	424 (52.6)	316.33	259 (32.1)	193.23	123 (15.3)	91.77
≥ 51	1,190 (8.2)	6,543.44	545	832.90	248 (45.5)	379.01	241 (44.2)	368.31	56 (10.3)	85.58
Ethnicity										
Han	5,109 (35.1)	43,477.78	1,987	457.02	968 (48.7)	222.64	513 (25.8)	117.99	506 (25.5)	116.38
Dai	5,122 (35.1)	42,597.15	2,574	604.27	1,288 (50.0)	302.37	667 (25.9)	156.58	619 (24.1)	145.31
Jingpo	3,626 (24.9)	29,808.51	1,843	618.28	845 (45.8)	283.48	486 (26.4)	163.04	512 (27.8)	171.76
Others	714 (4.9)	5,596.41	279	498.53	149 (53.4)	266.24	68 (24.4)	121.51	62 (22.2)	110.79
HIV transmission route										
Sexual contacts	8,068 (55.4)	64,770.10	2,242	346.15	1,225 (54.6)	189.13	684 (30.5)	105.60	333 (14.9)	51.41
Injection drug use	6,503 (44.6)	56,709.75	4,441	783.11	2,025 (45.6)	357.08	1,050 (23.6)	185.15	1,366 (30.8)	240.88
Diagnostic Year										
1989 - 2004	4,773 (32.8)	45,961.66	3,516	764.99	1,717 (48.8)	373.57	776 (22.1)	168.84	1,023 (29.1)	222.58
2005 - 2012	7,214 (49.5)	65,166.81	2,807	430.74	1,420 (50.6)	217.90	796 (28.4)	122.15	591 (21.0)	90.69
2013 - 2020	2,584 (17.7)	10,351.38	360	347.78	113 (31.4)	109.16	162 (45.0)	156.50	85 (23.6)	82.11
Baseline CD4 count, cells/μL										
0 ~ 100	1,719 (11.8)	16,644.38	591	355.07	345 (58.4)	207.28	153 (25.9)	91.92	93 (15.8)	55.87
101 ~ 200	1,896 (13.0)	19,929.60	507	304.61	216 (42.6)	129.77	181 (35.7)	108.75	110 (21.7)	66.09
201 ~ 350	3,056 (21.0)	33,422.33	618	371.30	195 (31.5)	117.16	254 (41.1)	152.60	169 (27.4)	101.54
> 350	2,580 (17.7)	23,803.94	296	177.84	41 (13.9)	24.63	149 (50.3)	89.52	106 (35.8)	63.69
Missing	5,320 (36.5)	27,679.60	4,671	2,806.35	2,453 (52.5)	1,473.77	997 (21.3)	599.00	1,221 (26.1)	733.58
Baseline viral load, log10 copies/mL										
0	3,458 (23.7)	35,641.25	429	120.37	106 (24.7)	29.74	197 (45.9)	55.27	126 (29.4)	35.35
> 0 and ≤ 3	1,356 (9.3)	15,509.01	239	154.10	80 (33.5)	22.45	107 (44.7)	30.02	52 (21.8)	14.59
> 3	2,111 (14.5)	21,647.26	511	236.06	238 (46.6)	66.78	174 (34.0)	48.82	99 (19.4)	27.78
Missing	7,646 (52.5)	48,682.33	5,504	1,130.60	2,826 (51.3)	792.90	1,256 (22.8)	352.40	1,422 (25.8)	398.98
Combination ART										
No	4,965 (34.1)	23,438.78	4,622	1,971.95	2,432 (52.6)	1,037.60	977 (21.1)	416.83	1,213 (26.2)	517.52
Yes	9,606 (65.9)	98,041.07	2,061	210.22	818 (39.7)	83.43	757 (36.7)	77.21	486 (23.6)	49.57

[a] Proportion among all-cause death.

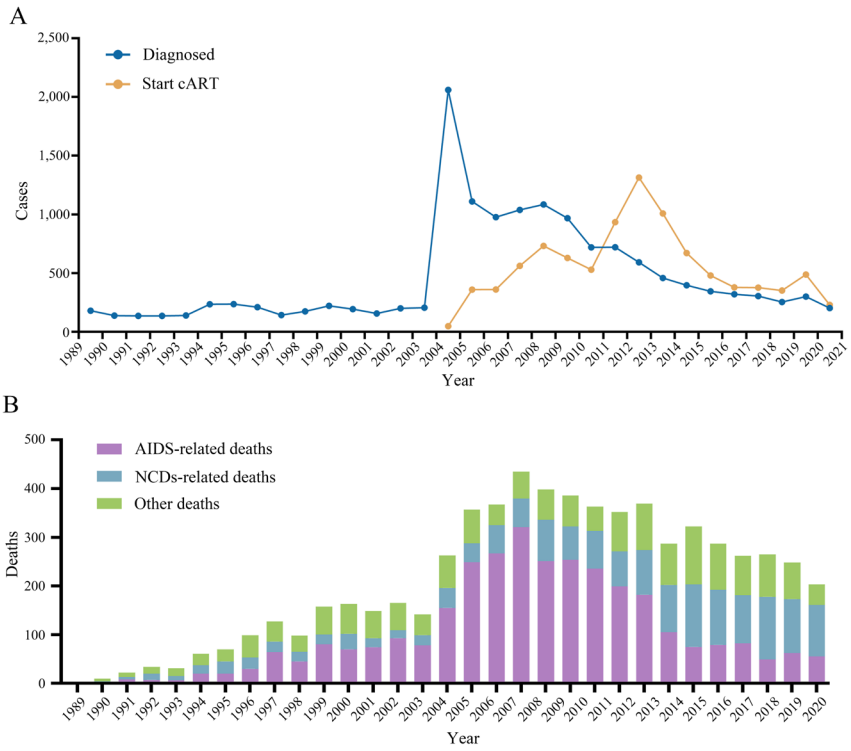

Figure 1. Annual number of HIV positive diagnoses, initiation of cART (A), and death (B) from 1989 to 2020 (deaths are classified by cause of death) in Dehong Prefecture, China.

Table 2. CD4 Test Index among HIV-infected patients in cART (*n* = 9,251)

Characteristics	Total (%)[a]	CD4 Test Index				χ^2	*p*
		≤0.3	> 0.3 and ≤ 0.8	> 0.8 and ≤ 1.2	> 1.2		
		N (%)[b]	*N* (%)[b]	*N* (%)[b]	*N* (%)[b]		
Total	9,251	1,342 (14.5)	1,914 (20.7)	4,571 (49.4)	1,424 (15.4)		
Gender						99.67	< 0.001
Male	6,044 (65.3)	937 (15.5)	1,399 (23.2)	2,793 (46.2)	915 (15.1)		
Female	3,207 (34.7)	405 (12.6)	515 (16.1)	1,778 (55.4)	509 (15.9)		
Age at ART initiation, yr						68.94	< 0.001
≤ 30	2,679 (29.0)	461 (17.2)	543 (20.3)	1,347 (50.3)	328 (12.2)		
31 ~ 40	3,593 (38.8)	447 (12.4)	746 (20.8)	1,843 (51.3)	557 (15.5)		
41 ~50	1,974 (21.3)	291 (14.7)	424 (21.5)	921 (46.7)	338 (17.1)		
≥ 51	1,005 (10.9)	143 (14.2)	201 (20.0)	460 (45.8)	201 (20.0)		
Ethnicity						117.02	< 0.001
Han	3,534 (38.2)	398 (11.3)	629 (17.8)	1,888 (53.4)	619 (17.5)		
Dai	3,042 (32.9)	471 (15.5)	693 (22.8)	1,452 (47.7)	426 (14.0)		
Jingpo	2,194 (23.7)	411 (18.7)	484 (22.1)	994 (45.3)	305 (13.9)		
Others	481 (5.2)	62 (12.9)	108 (22.5)	237 (49.3)	74 (15.4)		
HIV transmission route						106.46	< 0.001
Sexual contacts	6,462 (69.9)	877 (13.6)	1,194 (18.5)	3,396 (52.5)	995 (15.4)		
IDU	2,789 (30.1)	465 (16.7)	720 (25.8)	1,175 (42.1)	429 (15.4)		
Baseline CD4 count, cells/μL						253.10	< 0.001
0 ~ 100	1,719 (18.6)	248 (14.4)	240 (14.0)	950 (55.3)	281 (16.3)		
101 ~ 200	1,896 (20.5)	259 (13.7)	351 (18.5)	1,019 (53.7)	267 (14.1)		
201 ~ 350	3,056 (33.0)	373 (12.2)	617 (20.2)	1,641 (53.7)	425 (13.9)		
> 350	2,580 (27.9)	462 (17.9)	706 (27.4)	961 (37.2)	451 (17.5)		
Nadir CD4 count, cells/μL						175.32	< 0.001
0 ~ 100	1,420 (15.4)	261 (18.4)	264 (18.6)	684 (48.2)	211 (14.9)		
101 ~ 200	2,157 (23.3)	244 (11.3)	397 (18.4)	1,217 (56.4)	299 (13.9)		
201 ~ 350	2,924 (31.6)	351 (12.0)	568 (19.4)	1,552 (53.1)	453 (15.5)		
> 350	2,750 (29.7)	486 (17.7)	685 (24.9)	1,118 (40.7)	461 (16.7)		
Baseline viral load, log_{10} copies/mL						103.11	< 0.001
0	5,609 (60.6)	844 (15.0)	1,150 (20.5)	2,647 (47.2)	968 (17.3)		
> 0 and ≤ 3	1,545 (16.7)	198 (12.8)	244 (15.8)	872 (56.4)	231 (15.0)		
> 3	2,097 (22.7)	300 (14.3)	520 (24.8)	1,052 (50.2)	225 (10.7)		

[a] Frequency in the patients on cART; [b] Proportion among total.

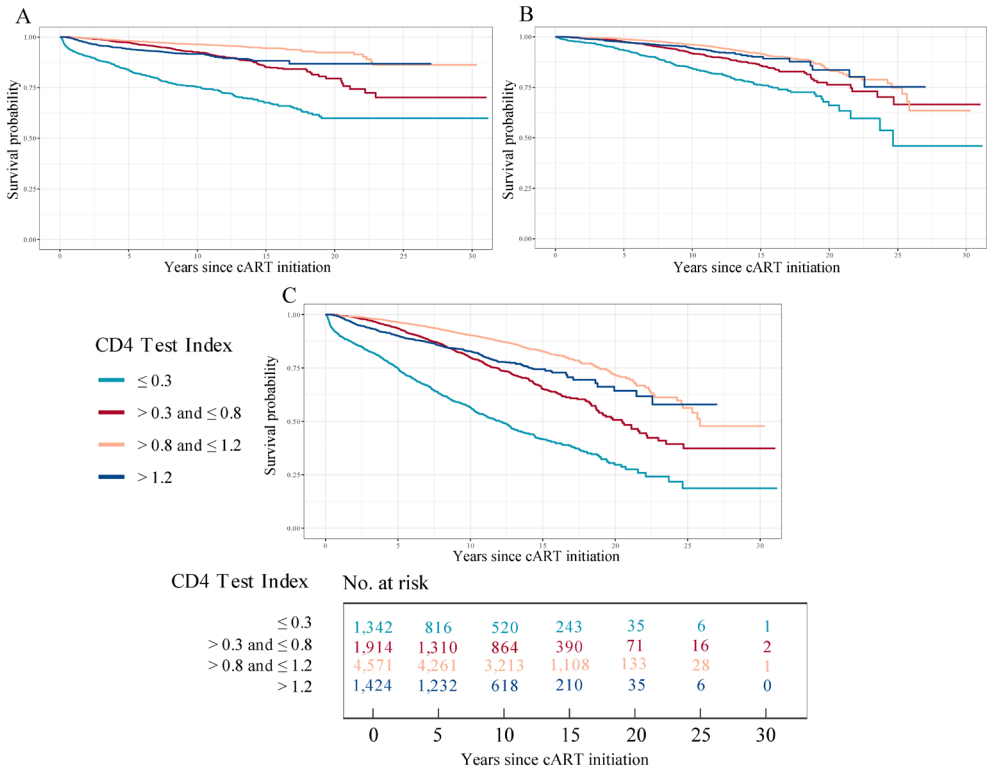

Figure 2. The Kaplan-Meier curve of AIDS-related cause (A), NCD-related causes (B), and all-cause (C) of death under CD4 test index.

Table 3. Univariate and multivariate COX analyses of factors associated with AIDS-related Deaths among HIV-infected patients with cART (*n* = 9,251)

Characteristics	Crude HR (95%*CI*)	*p*	Adjusted HR (95%*CI*)	*p*
Gender				
Male	1.00		1.00	
Female	0.45 (0.38, 0.53)	< 0.001	0.76 (0.63, 0.92)	0.005
Age at ART initiation, yr				
≤ 30	1.00		1.00	
31 ~ 40	1.33 (1.12, 1.59)	0.002	1.31 (1.09, 1.57)	0.004
41 ~50	1.47 (1.20, 1.79)	< 0.001	1.45 (1.18, 1.77)	< 0.001
≥ 51	1.53 (1.20, 1.95)	< 0.001	1.75 (1.36, 2.25)	< 0.001
Ethnicity				
Han	1.00		1.00	
Dai	1.17 (0.99, 1.38)	0.07	1.28 (1.08, 1.52)	0.004
Jingpo	1.31 (1.10, 1.56)	0.003	1.23 (1.02, 1.48)	0.028
Others	1.11 (0.80, 1.55)	0.54	1.13 (0.81, 1.57)	0.49
HIV transmission route				
Sexual relations	1.00		1.00	
IDU	2.16 (1.88, 2.48)	< 0.001	1.57 (1.34, 1.85)	< 0.001
Baseline CD4 count, cells/μL				
0 ~ 100	1.00		1.00	
101 ~ 200	0.54 (0.46, 0.64)	< 0.001	0.60 (0.50, 0.72)	< 0.001
201 ~ 350	0.29 (0.24, 0.35)	< 0.001	0.43 (0.35, 0.53)	< 0.001
> 350	0.10 (0.07, 0.13)	< 0.001	0.24 (0.17, 0.35)	< 0.001
Nadir CD4 count, cells/μL				
0 ~ 100	1.00		1.00	
101 ~ 200	0.36 (0.31, 0.43)	< 0.001	0.52 (0.43, 0.62)	< 0.001
201 ~ 350	0.20 (0.17, 0.24)	< 0.001	0.37 (0.30, 0.45)	< 0.001
> 350	0.06 (0.05, 0.08)	< 0.001	0.17 (0.12, 0.24)	< 0.001
CD4 Test Index				
≤ 0.3	1.00		1.00	
> 0.3 and ≤ 0.8	0.25 (0.21, 0.30)	< 0.001	0.18 (0.15, 0.22)	< 0.001
> 0.8 and ≤ 1.2	0.09 (0.08, 0.11)	< 0.001	0.06 (0.05, 0.07)	< 0.001
> 1.2	0.23 (0.19, 0.28)	< 0.001	0.17 (0.14, 0.21)	< 0.001
Baseline viral load, log_{10} copies/mL				
0	1.00		1.00	
> 0 and ≤ 3	5.00 (4.20, 5.96)	< 0.001	4.72 (3.94, 5.65)	< 0.001
> 3	3.83 (3.21, 4.56)	< 0.001	3.27 (2.73, 3.91)	< 0.001

Table 4. Univariate and multivariate COX analyses of factors associated with NCDs-related Deaths among HIV-infected patients with cART (*n* = 9,251)

Characteristics	Crude HR (95%*CI*)	*p*	Adjusted HR (95%*CI*)	*p*
Gender				
Male	1.00		1.00	
Female	0.42 (0.35, 0.50)	< 0.001	0.62 (0.51, 0.75)	< 0.001
Age at initiating, yr				
≤ 30	1.00		1.00	
31 ~ 40	1.92 (1.55, 2.40)	< 0.001	1.94 (1.55, 2.43)	< 0.001
41 ~50	2.85 (2.26, 3.60)	< 0.001	3.22 (2.54, 4.07)	< 0.001
≥ 51	5.38 (4.24, 6.82)	< 0.001	8.40 (6.56, 10.75)	< 0.001
Ethnicity				
Han	1.00		1.00	
Dai	1.37 (1.15, 1.64)	< 0.001	1.35 (1.13, 1.61)	0.001
Jingpo	1.62 (1.35, 1.96)	< 0.001	1.56 (1.28, 1.89)	< 0.001
Others	1.15 (0.79, 1.66)	0.47	1.24 (0.86, 1.80)	0.26
HIV transmission route				
Sexual relations	1.00		1.00	
IDU	2.39 (2.07, 2.77)	< 0.001	1.93 (1.62, 2.30)	< 0.001
Baseline CD4 count, cells/μL				
0 ~ 100	1.00		1.00	
101 ~ 200	1.04 (0.84, 1.29)	0.71	0.82 (0.65, 1.03)	0.090
201 ~ 350	0.88 (0.72, 1.08)	0.21	0.71 (0.56, 0.89)	0.003
> 350	0.83 (0.66, 1.05)	0.12	0.62 (0.46, 0.83)	0.001
Nadir CD4 count, cells/μL				
0 ~ 100	1.00		1.00	
101 ~ 200	0.89 (0.72, 1.10)	0.290	0.90 (0.72, 1.13)	0.36
201 ~ 350	0.77 (0.62, 0.95)	0.013	0.86 (0.68, 1.08)	0.20
> 350	0.66 (0.53, 0.83)	< 0.001	0.81 (0.61, 1.08)	0.15
CD4 Test Index				
≤ 0.3	1.00		1.00	
> 0.3 and ≤ 0.8	0.39 (0.32, 0.48)	< 0.001	0.30 (0.25, 0.38)	< 0.001
> 0.8 and ≤ 1.2	0.16 (0.13, 0.19)	< 0.001	0.13 (0.11, 0.16)	< 0.001
> 1.2	0.25 (0.19, 0.32)	< 0.001	0.18 (0.14, 0.24)	< 0.001
Baseline viral load, log_{10} copies/mL				
0	1.00		1.00	
> 0 and ≤ 3	0.73 (0.59, 0.90)	0.004	0.84 (0.68, 1.05)	0.12
> 3	0.96 (0.80, 1.14)	0.64	0.95 (0.79, 1.14)	0.56

(aHR = 0.06; 95%*CI*: 0.05-0.07), or > 1.2 (aHR = 0.17; 95%*CI*: 0.14-0.21) were at lower risk of AIDS-related death.

3.4.3. Associates of NCDs-related mortality

As shown in Table 4, univariate COX regression analysis indicated that the NCDs-related mortality was significantly associated with sex, age, ethnicity, HIV transmission route, nadir CD4 count, baseline HIV viral load, and CD4 test index. In multivariate COX regression analysis adjusting for confounding variables, NCDs-related mortality remained significantly associated with sex, age, ethnicity, HIV transmission route, and CD4 test index, but was no longer associated with nadir CD4 count and baseline HIV viral load. In particular, compared to patients with CD4 test index less than 0.3, patients with CD4 test index at 0.3-0.8 (aHR = 0.30, 95%*CI*: 0.25-0.38), 0.8-1.2 (aHR = 0.13; 95%*CI*: 0.11-0.16), or > 1.2 (aHR = 0.18; 95%*CI*: 0.14-0.24) were at lower risk of NCDs-related death.

4. Discussion

Our findings show that, as one of the earliest epicenters affected by HIV in China, although the annual number of deaths among HIV-infected people in Dehong Prefecture has been declining, the mortality here is still higher than in high-income countries (*21,22*). Among patients with cART, the median CD4 test index was 1.0 (IQR 0.6-1.3), and 35.2% had a CD4 test index less than 0.8 and the CD4 test index was significantly different by sex, age, ethnicity, HIV transmission route, baseline CD4 count, nadir CD4 count, and baseline HIV viral load. Patients who complied with routine CD4 testing had the lowest risk of both AIDS-related and NCDs-related deaths.

This study, for the first time, evaluated the impact of compliance with routine CD4 testing on all-cause mortality of PWH in China. A CD4 test index was developed and if over 0.8, indicates that the patients have well adhered to routine CD4 testing and have substantially reduced risks of deaths, whereas a lower CD4 test index was significantly associated with higher risk of death. However, it was the CD4 test index between 0.8 and 1.2 but not over 1.2 that was significantly linked to the lowest risk of both AIDS-related and NCDs-related deaths. This observation has two important implications. One is that routine CD4 monitoring is critical for survival of PWH, as many reports have demonstrated that routine CD4 testing helps healthcare providers monitor the immunodeficiency

status, understand the disease progression, and effectively improve the quality of life of HIV-infected patients (*23*). The other, however, is that an appropriate (once per 6 months or at least once a year) rather than an unnecessarily higher frequency of routine CD4 testing could be most cost-effective in reducing mortality of HIV patients. This is particularly relevant in resource-limited settings. In fact, there is literature showing that enriching the content and reducing the frequency of a single CD4 test could achieve a balance between decreasing the risk of death and saving health service resources, and reduces the economic burden of HIV disease in LMIC (*13,24*). According to the China national guidelines for cART, blood biochemical tests for aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), triglyceride (TG), creatinine (Cr), blood urea nitrogen (BUN), total bilirubin, and glucose (Glu) were preformed simultaneously with CD4 test, which would not only help monitoring side effects of cART but also assessing risks of certain NCDs.

cART was not available until 2003 in China when the government launched the national comprehensive anti-HIV/AIDS campaign including NFATP. In the pre-ART era, AIDS-related death was a major health threat for PWH (*25*). However, with the expansion of the combination ART and increasing life expectancy, the prevalence of NCDs among PWH in China has been increasing and AIDS-related deaths have been replaced by NCDs-related deaths as the main threat for PWH (*26*). In the present study, the main cause of deaths among PWH was also shifted from AIDS-related severe immunodeficiency during the early non-ART stage to non-AIDS-related diseases especially NCDs in the past decade. NCDs have become a great challenge for HIV-infected individuals and health care providers in China and other LMIC, which calls for integration of NCDs prevention, intervention and treatment into the existing anti-HIV/AIDS campaigns.

Nadir CD4 count and baseline viral load were significantly associated with AIDS-related deaths but not with NCDs-related deaths. The increasing lifespan of patients in Dehong Prefecture increased risks to NCDs and NCDs-related deaths, as patients were more likely to be exposed to unhealthy diets and harmful use of alcohol and tobacco (*27,28*). In addition, cART side effects predispose individuals further to NCDs and NCDs-related deaths (*29*).

Several published studies have shown correlation between gender and risk of death in HIV-infected patients (*30,31*). Women had lower risks of both AIDS-related and NCDs-related deaths than men in the present study. This is most likely because women have had better adherence to cART, lower prevalence of alcohol use and injection drug use (*32-35*). Other pathophysiological differences by sex are not ruled out and deserve further investigation.

The Dai ethnic patients have the highest AIDS-related mortality whereas the Jingpo ethnic patients have the highest NCDs-related mortality in this study. Previous studies in Dehong Prefecture found that smoking and heavy drinking were more prevalent among Jingpo patients (*35,36*). Whether there are genetic predisposing factors and gene-environment interactions for differential morbidities and mortalities between different ethnicities remains to be investigated in the near future.

This study is subject to several limitations. First, behavioral and environmental exposures to non-AIDS diseases especially NCDs were not systematically collected, refraining us from examining secular trends of such exposures and fully understanding the rising of NCDs-related deaths over the past decades. Second, although the causes of deaths were carefully investigated and verified by the researchers, misclassifications could still not be ruled out given that the study site is a remote rural area in Southwestern China where access to and utilization of health services for non-AIDS diseases were relatively limited, especially for those living in rural villages. Most likely, some HIV-infected patients died of NCDs might have never been diagnosed with NCDs and thus were not correctly attributed to NCDs-related deaths, underestimating the NCDs-related mortality. Third, the required frequency of routine CD4 testing for HIV-infected patients, although mostly twice per year, was not unanimous over the study period. However, according to the study results, an appropriate frequency of routine CD4 testing instead of too less or too more tests should be the best recommendation.

5. Conclusion

In conclusion, NCDs-related deaths have taken over as the main causes of death among treated PWH in rural China. Sex, age, ethnicity, HIV transmission route, baseline CD4 count, nadir CD4 count, and baseline HIV viral load were associated with the compliance level of CD4 test. PWH benefit from long-term compliance with appropriate routine CD4 monitoring in controlling all-cause mortality. Our study will provide new experience to routine HIV surveillance and testing in LMIC, that is, enriching the content and reducing the frequency (once per 6 months or at least once a year) of CD4 test could best reduce the burden of HIV disease. In addition, risk assessment and intervention, diagnosis and treatment of NCDs especially those common to HIV patients are urgently needed to be integrated into the existing comprehensive anti-HIV/AIDS programs.

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