Letter to the Editor

Benefits of Early and Immediate Initiation of Antiretroviral Therapy among HIV Patients in Chongqing, China*

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In an effort to end the HIV epidemic by 2030, the Joint United Nations Program on HIV/AIDS (UNAIDS) set the '90-90-90' target and aimed to expand the timely use of ART worldwide. By the end of 2017, 21.7 million people living with HIV, amounting to 59% of HIV patients worldwide, were receiving antiretroviral therapy (ART)[1]. In China, the National Free Antiretroviral Treatment Program (NFATP), which was initiated in 2002, continued to progress. Following updated WHO ART guidelines, the national ART eligibility criterion for CD4 counts was gradually relaxed from < 200 cells/mm^3 to < 350 cells/mm^3 in 2008, and to < 500 cells/mm^3 in 2015. Finally, ART was recommended for all HIV patients nationwide, irrespective of CD4 counts in early 2016[2].

Early ART is defined as initiating ART at high CD4 counts (≥ 500 cells/mm^3), while immediate ART focuses on rapid ART initiation following HIV diagnosis (i.e., within 30 d)[3]. These two major determinants of ART initiation timing are associated with treatment outcomes. Evidently, early ART may benefit HIV patients by enhancing viral suppression and survival[4]. However, some studies reported that early ART may increase the risk of dropout during treatment[5]. Immediate initiation of ART reduced the duration of high-level viral loads carried by HIV patients, and therefore it was adopted as a strategy for enhancing the global effort to control the HIV epidemic and optimize the health of those living with HIV[6]. However, in real-world settings, late or delayed treatment is frequently encountered, especially in developing countries.

This observational cohort study was conducted in Chongqing, a city with a serious HIV epidemic in southwest China. Based on the large ART database, we evaluated the effects of both pre-ART CD4 counts and duration from diagnosis to ART initiation, on treatment outcomes. Individuals included in this cohort were those who newly initiated ART between 2013 and 2017. The eligibility criteria of this study included the following, being 18 years or older at ART initiation, having follow-up records, accepting treatment the first time and having pre-ART CD4 count records. Observations began on the date of ART initiation and terminated on December 31, 2018. All patients signed an informed consent form at the time of ART initiation.

Variables collected at baseline enrollment for treatment included age, sex, marital status, transmission route, WHO clinic stage before ART, initial ART regimen, year of ART initiation, pre-ART CD4 counts, and duration from diagnosis to ART. Variables collected at each follow-up included duration of ART, death, dropout, and viral load (VL). Death measure was all-cause mortality. Dropout events were defined as cessation of ART, or loss of follow-up at least one time, among the surviving patients. For those who had withdrawn more than once, the last dropout follow-up date was selected. The censoring events included both survival at terminal time and termination for other reasons. Virologic failure was defined as VL ≥ 200 copies/mL at 12 (range 9–15) months following ART initiation[7]. For those who had more than one VL result, the result closest to the 12-month test date was selected. Cox proportional hazards regression model

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was used to evaluate effects on death and dropout. Logistic regression model was used to assess determinants of virologic failure. All statistical analyses were performed using IBM SPSS Statistics, Version 19.0, IBM Corp., Armonk, NY, USA. This study was approved by the Institutional Review Board of Chongqing CDC. All records utilized in the analysis were anonymous and did not contain any personal identifiers.

A total of 25,431 HIV patients were found to be eligible for inclusion in the study cohort. Characteristics of the cohort are shown in Supplementary Table S1 (available in www.besjournal.com). The percentage of patients with pre-ART CD4 counts < 350 cells/mm^3, 350–499 cells/mm^3, and ≥ 500 cells/mm^3 was 75.9%, 17.5%, and 6.6%, respectively. Furthermore, 46.0% of the patients initiated ART within 30 d following HIV diagnosis, 22.7% initiated ART between 31 and 90 d, 12.9% initiated ART between 91 and 365 d and 18.4% initiated ART after 365 d.

A total of 2,102 deaths was reported during the observation period. The overall mortality rate was 3.0 per 100 person years (PY). Adjusted effects of pre-ART CD4 counts and duration from diagnosis to ART on death are presented (Table 1). Compared with CD4 counts < 350 cells/mm^3 group, initiating ART at higher CD4 counts reduced the risk of death (350–499 cells/mm^3: AHR = 0.8; ≥ 500 cells/mm^3: AHR = 0.7). Compared with immediate ART (within 30 d), delayed ART showed a higher risk of death (91–365 d: AHR = 1.2; > 365 d: AHR = 1.5).

Our study showed that both early ART initiation and immediate ART initiation were significantly associated with mortality reduction. Consistent with our study, research studies definitively revealed that early and immediate initiation of ART meaningfully improved survival[8-9]. Furthermore, in Chongqing, less than 10% of the patients initiated ART early, while less than 50% started ART immediately. CD4 threshold limitations and late diagnoses may have led to delays in presenting for treatment during the 2013–2017 period[2,10]. In order to improve late ART initiation, early HIV diagnosis must be made feasible and those groups who present for late treatment should be focused on.

A total of 3,257 HIV patients dropped out of treatment, and the overall dropout rate was 4.6 per 100 PY. Compared with CD4 counts of < 350 cells/mm^3 group, higher CD4 count groups exhibited a higher risk of dropout (350–499 cells/mm^3: AHR = 1.3; ≥ 500 cells/mm^3: AHR = 1.5). Compared with immediate ART, delayed ART increased the dropout rate (31–90 d: AHR = 1.3; 91–365 d: AHR = 1.9; > 365 d: AHR = 2.2) (Table 1). A further analysis by stratification presented that immediate ART had much lower rate of dropout than delayed ART (91–365 d: AHR = 2.3; > 365 d: AHR = 2.9) among HIV patients with CD4 counts ≥ 500 cells/mm^3 (Supplementary Table S2 available in www.

Table 1. Effects of pre-ART CD4 counts and duration from diagnosis to ART on death and dropout among HIV patients

Variables	Number (person years)	Death				Dropout			
		Number	Mortality rate per 100 PY (95% *CI*)	AHR (95% *CI*)	*P* value	Number	Dropout rate per 100 PY (95% *CI*)	AHR (95% *CI*)	*P* value
Overall	25,431 (70970.6)	2,102	3.0 (2.8, 3.1)			3,257	4.6 (4.4, 4.7)		
Pre-ART CD4 counts (cells/mm^3)									
< 350	19,305 (54580.8)	1,870	3.4 (3.3, 3.6)	1.0		2,331	4.3 (4.1, 4.4)	1.0	
350–499	4,451 (12306.3)	174	1.4 (1.2, 1.6)	0.8 (0.6, 0.9)	0.001	654	5.3 (4.9, 5.7)	1.3 (1.1, 1.4)	< 0.001
≥ 500	1,675 (4083.5)	58	1.4 (1.1, 1.8)	0.7 (0.5, 0.9)	0.010	272	6.7 (5.9, 7.4)	1.5 (1.3, 1.7)	< 0.001
Duration from diagnosis to ART (d)									
≤ 30	11,704 (31232.5)	932	3.0 (2.8, 3.2)	1.0		939	3.0 (2.8, 3.2)	1.0	
31–90	5,770 (16919.6)	489	2.9 (2.6, 3.1)	1.1 (1.0, 1.2)	0.088	636	3.8 (3.5, 4.0)	1.3 (1.2, 1.5)	< 0.001
91–365	3,280 (9708.5)	276	2.8 (2.5, 3.2)	1.2 (1.1, 1.4)	0.002	562	5.8 (5.3, 6.3)	1.9 (1.7, 2.1)	< 0.001
> 365	4,677 (13110.0)	405	3.1 (2.8, 3.4)	1.5 (1.3, 1.6)	< 0.001	1,120	8.5 (8.1, 9.0)	2.2 (2.0, 2.5)	< 0.001

Note. *CI*, confidence interval; AHR, adjusted hazard ratio; Covariates of the adjusted model included: age, sex, marital status, transmission route, WHO clinic stage before ART, initial ART regimen, year of ART initiation.

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We found that early ART initiation was associated with a greater probability of dropout. There is an ongoing debate regarding adherence to treatment by those undergoing early ART. Some researchers have indicated the presence of a greater risk for treatment cessation among patients with high pre-ART CD4 counts[5]. However, others contend that patient preparedness being critical for ART adherence is not evidence based, and therefore ART should not be delayed[6]. But the stratification analysis of our study indicated that encouraging patients to initiate ART immediately regardless of CD4 counts may be a good approach to reduce dropout.

Of 11,974 HIV patients who underwent VL testing at 12 months (range 9–15) following ART initiation, a total of 977 patients (8.2%) exhibited virologic failure. Compared with the CD4 counts of < 350 cells/mm^3, starting ART at higher CD4 counts decreased the risk of virologic failure (350–499 cells/mm^3: AOR = 0.7). Compared with immediate ART, delayed ART induced a higher risk of virologic failure (91–365 d: AOR = 1.2; > 365 d: AOR = 1.5) (Table 2).

The results of the current study indicated that initiating ART at higher pre-ART CD4 counts, or immediately (within 30 d) following diagnosis, decreased the rate of virologic failure. In our study, early ART (CD4 counts ≥ 500 cells/mm^3) had a lower virologic failure rate compared with pre-ART CD4 counts < 350 cells/mm^3 (6.6% *vs*. 9.0%). However, the virologic failure rate of early ART was higher than that in those with 350–499 cells/mm^3 (6.6% *vs*. 5.0%), which may have been caused by the higher dropout rate in the ≥ 500 cells/mm^3 group. If initiating ART late, patients would carry high viral load levels for a longer time, leading to a higher probability for HIV transmission to partners. Therefore, early and immediate ART initiation may provide many short- and long-term benefits for HIV patients as well as the for public health (Table 2).

Our study was subject to some limitations, e.g. about 10% of cases were excluded in our study due to without pre-ART CD4 counts, and less than half of individuals testing VL at 12 (range 9–15) months remained in our data to assess determinants of virologic failure. These limitations could influence assessment results.

In summary, our findings indicated that initiating ART early and immediately is important for reducing the risk of mortality and virologic failure. To achieve the UNAIDS targets for ending the HIV epidemic, continued efforts are needed to enhance the early diagnosis process and treat all diagnosed HIV patients without delay regardless of CD4 counts. Although patients with high pre-ART CD4 counts showed a greater risk of dropout, shortening the interval from diagnosis to ART may help reduce dropout effectively.

We thank all healthcare providers across Chongqing municipality for their contribution to collection of follow-up data from ART clinics. We are also grateful to all the staff involved in experiments.

Table 2. Effects of pre-ART CD4 counts and duration from diagnosis to ART on virologic failure among HIV patients

Variables	Number	Number of virologic failure	% (95% *CI*)	*OR* (95% *CI*)	*P* value	AOR (95% *CI*)	*P* value
Overall	11,974	977	8.2 (7.7, 8.6)				
Pre-ART CD4 counts (cells/mm^3)							
< 350	9,152	824	9.0 (8.4, 9.6)	1.0		1.0	
350–499	2,068	103	5.0 (4.0, 5.9)	0.5 (0.4, 0.7)	< 0.001	0.7 (0.5, 0.8)	< 0.001
≥ 500	754	50	6.6 (4.9, 8.4)	0.7 (0.5, 1.0)	0.028	0.9 (0.6, 1.2)	0.356
Duration from diagnosis to ART (d)							
≤ 30	5,744	421	7.3 (6.7, 8.0)	1.0		1.0	
31–90	2,761	210	7.6 (6.6, 8.6)	1.0 (0.9, 1.2)	0.649	1.1 (0.9, 1.3)	0.582
91–365	1,473	128	8.7 (7.2, 10.1)	1.2 (1.0, 1.5)	0.079	1.2 (1.0, 1.5)	0.043
> 365	1,996	218	10.9 (9.6, 12.3)	1.6 (1.3, 1.8)	< 0.001	1.5 (1.2, 1.8)	< 0.001

Note. *CI*, confidence interval; *OR*, odds ratio; AOR, adjusted odds ratio; covariates of the adjusted model included: age, sex, marital status, transmission route, WHO clinic stage before ART, initial ART regimen, year of ART initiation.

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REFERENCES

1. The Joint United Nations Program on HIV/AIDS. Global HIV & AIDS statistics — 2018 fact sheet. UNAIDS, 2018. Available at: https://www.unaids.org/en/resources/fact-sheet. [2019-7-15]
2. Ma Y, Dou Z, Guo W, et al. The human immunodeficiency virus care continuum in China: 1985–2015. Clin Infect Dis, 2018; 66, 833–9.
3. Zhao Y, McGoogan JM, Wu Z. The benefits of immediate ART. J Int Assoc Provid AIDS Care, 2019; 18, 2325958219831714.
4. Fatti G, Grimwood A, Nachega JB, et al. Better virological outcomes amongst people living with HIV initiating early antiretroviral treatment (CD4 counts ≥ 500 cells/μL) in the HPTN 071 (PopART) trial in south Africa. Clin Infect Dis, 2019; ciz214.
5. Tang Z, Pan SW, Ruan Y, et al. Effects of high CD4 cell counts on death and attrition among HIV patients receiving antiretroviral treatment: an observational cohort study. Sci Rep, 2017; 7, 3129.
6. Boyd MA, Boffito M, Castagna A, et al. Rapid initiation of antiretroviral therapy at HIV diagnosis: definition, process, knowledge gaps. HIV Med, 2019; 20(Suppl 1), 3–11.
7. Chinese Medical Association, Chinese Center for Disease Control and Prevention. Guidelines for diagnosis and treatment of HIV/AIDS in China (2018). Chin J AIDS STD, 2018; 24, 1266–82.
8. Mangal TD, Meireles MV, Pascom ARP, et al. Determinants of survival of people living with HIV/AIDS on antiretroviral therapy in Brazil 2006–2015. BMC Infect Dis, 2019; 19, 206.
9. Zhao Y, Wu Z, McGoogan JM, et al. Immediate antiretroviral therapy decreases mortality among patients with high CD4 counts in China: a nationwide, retrospective cohort study. Clin Infect Dis, 2018; 66, 727–34.
10. Tang H, Mao Y, Tang W, et al. 'Late for testing, early for antiretroviral therapy, less likely to die': results from a large HIV cohort study in China, 2006-2014. BMC Infect Dis, 2018; 18, 272.

Supplementary Table S1. Characteristics of HIV patients initiating ART between 2013 and 2017 in Chongqing, China

Variables	Entire study cohort, *n* (%)	Pre-ART CD4 counts groups, *n* (%)			*P* value
		< 350 cells/mm^3	350–499 cells/mm^3	≥ 500 cells/mm^3	
Total	25,431 (100.0)	19,305 (100.0)	4,451 (100.0)	1,675 (100.0)	
Age (years)					< 0.001
18–34	7,633 (30.0)	5,119 (26.5)	1,822 (40.9)	692 (41.3)	
35–49	7,659 (30.1)	5,922 (30.7)	1,266 (28.4)	471 (28.1)	
≥ 50	10,139 (39.9)	8,264 (42.8)	1,363 (30.6)	512 (30.6)	
Sex					0.083
Male	19,204 (75.5)	14,521 (75.2)	3,419 (76.8)	1,264 (75.5)	
Female	6,227 (24.5)	4,784 (24.8)	1,032 (23.2)	411 (24.5)	
Marital status					< 0.001
Single	6,605 (26.0)	4,491 (23.3)	1,528 (34.3)	586 (35.0)	
Married	14,371 (56.5)	11,260 (58.3)	2,262 (50.8)	849 (50.7)	
Divorced/Separated/Widowed/Unknown	4,455 (17.5)	3,554 (18.4)	661 (14.9)	240 (14.3)	
Transmission route					< 0.001
Heterosexual contact	17,023 (66.9)	13,357 (69.2)	2,681 (60.2)	985 (58.8)	
Homosexual contact	5,467 (21.5)	3,658 (18.9)	1,324 (29.7)	485 (29.0)	
Injection drug use	1,017 (4.0)	749 (3.9)	188 (4.2)	80 (4.8)	
Blood transfusion or Unknown	1,924 (7.6)	1,541 (8.0)	258 (5.8)	125 (7.5)	
WHO clinic stage before ART*					< 0.001
I/II	10,985 (43.2)	5,917 (30.7)	3,686 (82.8)	1,382 (82.5)	
III/IV	14,446 (56.8)	13,388 (69.3)	765 (17.2)	293 (17.5)	
Initial ART regimen					< 0.001
TDF included first-line regimen	21,652 (85.2)	16,286 (84.4)	3,881 (87.2)	1,485 (88.7)	
AZT included first-line regimen	3,318 (13.0)	2,636 (13.7)	521 (11.7)	161 (9.6)	
LPV/r included second-line regimen	292 (1.1)	227 (1.2)	40 (0.9)	25 (1.5)	
Regimen out of recommendations	169 (0.7)	156 (0.8)	9 (0.2)	4 (0.2)	
Year of ART initiation					< 0.001
2013	3,611 (14.2)	3,189 (16.5)	338 (7.6)	84 (5.0)	
2014	4,925 (19.4)	3,843 (19.9)	842 (18.9)	240 (14.3)	
2015	5,801 (22.8)	3,991 (20.7)	1,404 (31.5)	406 (24.2)	
2016	5,507 (21.6)	4,060 (21.0)	986 (22.2)	461 (27.5)	
2017	5,587 (22.0)	4,222 (21.9)	881 (19.8)	484 (28.9)	
Duration from diagnosis to ART (d)					< 0.001
≤ 30	11,704 (46.0)	9,519 (49.3)	1,615 (36.3)	570 (34.0)	
31–90	5,770 (22.7)	4,467 (23.1)	936 (21.0)	367 (21.9)	
91–365	3,280 (12.9)	2,337 (12.1)	693 (15.6)	250 (14.9)	
> 365	4,677 (18.4)	2,982 (15.4)	1,207 (27.1)	488 (29.1)	

Note. WHO clinical stages I/II: asymptomatic period or mild symptomatic period, WHO clinical stages III/IV: moderate symptomatic period, or typical AIDS period; TDF, Tenofovir; AZT, Zidovudine; LPV/r, Lopinavir/Ritonavir.

Supplementary Table S2. Effects of duration from diagnosis to ART on dropout stratified by pre-ART CD4 counts groups

Duration from diagnosis to ART (d)	< 350 cells/mm^3			350–499 cells/mm^3			≥ 500 cells/mm^3		
	Dropout rate per 100 PY	AHR (95% *CI*)	*P* value	Dropout rate per 100 PY	AHR (95% *CI*)	*P* value	Dropout rate per 100 PY	AHR (95% *CI*)	*P* value
≤ 30	3.0	1.0		3.0	1.0		3.5	1.0	
31–90	3.7	1.3 (1.2, 1.4)	< 0.001	4.0	1.5 (1.2, 1.9)	0.002	4.4	1.4 (0.9, 2.2)	0.202
91–365	5.6	1.9 (1.7, 2.1)	< 0.001	5.7	2.0 (1.5, 2.5)	< 0.001	7.9	2.3 (1.5, 3.4)	< 0.001
> 365	7.9	2.1 (1.8, 2.3)	< 0.001	9.3	2.4 (1.9, 2.9)	< 0.001	11.6	2.9 (2.1, 4.2)	< 0.001

Note. PY, person years; *CI*, confidence interval; AHR, adjusted hazard ratio; covariates of the adjusted model included: age, sex, marital status, transmission route, WHO clinic stage before ART, initial ART regimen, year of ART initiation.