

# HIV disease progression among heterosexually-infected individuals before the introduction of universal ART in China: A linear mixed-effects model

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**Abstract:** In 2016, China introduced universal antiretroviral therapy (ART) for all HIV-infected individuals regardless of CD4 cell count. However, the natural history and rate of CD4 count decline among heterosexually-infected individuals remain uncharacterized. Analyzing national surveillance data can address this gap and shed light on the pathogenesis of HIV in this population. We used a linear mixed-effects model to assess CD4 trajectory over time before ART initiation and estimated the median time from HIV seroconversion to reaching CD4 thresholds of < 500, < 350, and < 200 cell/mm<sup>3</sup>. From the Chinese HIV/AIDS Comprehensive Response Information Management System, 59,085 eligible individuals were identified, with 113 having data to estimate the date of HIV seroconversion. The linear mixed-effects models estimated an intercept of 23.64 (95% confidence interval [CI]: 22.41 to 24.87) and a slope of -1.32 (95% CI: -1.34 to -1.30) for males, and an intercept of 22.70 (95% CI: 21.00 to 24.40) and a slope of -1.29 (95% CI: -1.31 to -1.27) for females. The estimated median times from HIV seroconversion to reaching CD4 count thresholds of < 500, < 350, < 200 cells/mm<sup>3</sup> were 0.97, 3.74, and 7.20 years for males, and 0.26, 3.09, and 6.48 years for females, respectively. Males consistently took longer to reach these CD4 count thresholds compared to females of the same age group. Older individuals ( $\geq 40$  years) reached CD4 thresholds faster than younger individuals (15-29 years), indicating more rapid disease progression in older people living with HIV.

**Keywords:** HIV/AIDS, disease progression, CD4<sup>+</sup> T cell count, linear mixed-effects model

## Introduction

HIV remains a major public health issue globally and in China. By the end of 2019, approximately 37.9 million people were living with HIV (PLHIV) worldwide (1). In China, an estimated 1.25 million people were living with HIV in 2018, with 73.1% infected through heterosexual contact (2,3). Effective clinical and public health management rely on accurate estimates of new HIV infections and their distribution by factors such as age, sex, and transmission mode. Understanding the natural history of HIV/AIDS and its disease progression is essential for this purpose (4).

The most renowned study on the natural history of HIV, conducted by Fauci and colleagues in 1996, showed that the rate of CD4 level decline decreases over time before antiretroviral therapy (ART) initiation based on clinical assessments and laboratory measurements of CD4 counts and virus loads (5). Similar studies (6-8) have been conducted in low and middle-income regions, as well as in Europe and the

United States, involving cohorts of individuals with HIV not on ART (9-11). However, no such studies have been conducted in China (12).

In 2015, World Health Organization (WHO) recommended ART for all PLHIV regardless of CD4 level. China adopted this policy in the national treatment guideline in June 2016 (13). Understanding the natural history of HIV infection and disease progression in China has become challenging since the implementation of the "treat-all" policy.

CD4 cell count is a crucial biomarker for studying HIV disease progression and prognosis (14,15). The rate of CD4 decline since infection can be used in statistical models to estimate HIV incidence (5). Two back-calculation methods have been developed for estimating the rate of decline of CD4 count: a multi-state modelling method and a CD4 depletion modelling method. The multi-state model categorizes HIV infections by CD4 level (16,17), while the CD4 depletion model uses longitudinal data of individually repeated measurements of CD4 count before ART

initiation in a linear mixed-effects model (4,7,18).

Advantages of the CD4 depletion modelling method include: *i*) handling correlation between CD4 measurements without assuming independence; *ii*) not requiring complete historic data on HIV diagnoses, which is useful when there are fewer CD4 counts available in the early years of a study (19); and (3) back-calculating seroconversion time for each individual, describing the distribution of new infections over a calendar year. These advantages enable the estimation of new HIV infections in China and the time from seroconversion to various CD4 cell count thresholds.

To our knowledge, and based on a systematic literature search in PubMed, Embase, Web of Science, and Chinese database, no published studies have addressed the natural history and disease progression indicated by the rate of decline in CD4 cell count among heterosexually infected HIV patients in China. Using data from the Chinese HIV/AIDS Comprehensive Response Information Management System (CRIMS), we conducted an analysis of heterosexually-infected patients and applied a linear mixed-effects model (adapted from the CD4 depletion modelling method) to estimate the rate of CD4 decline before ART initiation and the time from HIV seroconversion to CD4 cell count thresholds of < 200, < 350, < 500 cell/mm<sup>3</sup>.

## Patients and Methods

### Data source and study population

HIV has been a notifiable infectious disease in China since 1985. Established in 2005, CRIMS is an integrated internet-based system for real-time collection and reporting of newly diagnosed HIV/AIDS cases in China. Local physicians and health professionals report newly diagnosed HIV/AIDS cases to CRIMS using a uniform case reporting form (CRF) that includes personal information, such as date of birth, sex, residence, occupation, date of diagnosis, and testing results. All cases are validated by local clinicians and uploaded to China CDC for analysis and monitoring.

Eligible subjects included all HIV cases reported to CRIMS who met the following criteria: *i*) diagnosed with HIV between January 2006 and May 2019 (as the reporting quality in CRIMS improved starting in January 2006; *ii*) aged 15 years or older at the time of diagnosis; *iii*) self-reported infection through heterosexual contact; and *iv*) had at least two CD4 measurements before ART initiation. Exclusion criteria included incomplete records and non-citizens of China.

### Statistical Methods

CD4 counts are periodically measured in PLHIV in China. We used these periodic assessments to construct

an analytic dataset with CD4 counts over time for each subject. A linear mixed-effects model with random slope and/or random intercept was used to fit variations within and between individuals' CD4 measurements (20).

The study included three key variables: *i*) seroconversion date, estimated as the midpoint between last negative HIV test date and the first positive test date within a three-year interval; *ii*)  $t_1$ , the interval between the HIV seroconversion date and each CD4 test date, used as the independent variable in the initial regression  $\sqrt{\text{CD4}} = a + b \cdot t_1$ ; and *iii*)  $t_2$ , the intervals between the first CD4 test date and subsequent CD4 test dates, used as the independent variable in the second regression  $\sqrt{\text{CD4}} = a' + b' \cdot t_2$ .

The model fit the square root of CD4 over time:  $\sqrt{\text{CD}_4(t)} = a_i + (b_i \times t)$  (5,19), where the variable  $t$  denotes time from date of infection to CD4 test date. We first estimated the intercept ( $a_i$ ), the average square root of CD4 count at the date of seroconversion, and the slope ( $b_i$ ), the rate of change in the square root of CD4 count over time. In the initial regression,  $\sqrt{\text{CD4}} = a + b \cdot t_1$ ,  $a$  was treated as a fixed intercept (assuming all individuals had the same CD4 count at time of seroconversion), and  $b$  as either fixed or random. Fixed  $b$  values were expected to be close to the mean of random  $b$  and fixed  $b'$ . The fixed  $b'$  values were estimated using data from all individuals in the second regression,  $\sqrt{\text{CD4}} = a' + b' \cdot t_2$ . In this regression,  $b'$  was treated as a fixed slope (assuming all individuals had the same depletion rate), and  $a'$  as a random intercept (each person had a different value of CD4 count on the first CD4 test date). Assuming linearity in the CD4 depletion model during the study period,  $b$  and  $b'$  should be statistically equivalent. However,  $a$  and  $a'$  are different (with  $a > a'$ ).

We used the model to estimate the time from seroconversion to reaching CD4 cell count thresholds of < 200, < 350, < 500 cell/mm<sup>3</sup> to assess disease progression among men who have sex with women (MSW) and women who have sex with men (WSM).

Analyses were performed using SAS 9.4 (Statistical Analysis Software 9.4, SAS Institute Inc, Cary, North Carolina, USA). All tests were two-tailed with  $p$  values of 0.05 or less considered statistically significant.

### Ethical review

The study was approved by the Ethics Committee of the National Centers for STD/AIDS Prevention and Control, China CDC (Ethical approval number: X190311565).

## Results and Discussion

Our analytic dataset included 59,085 eligible cases. Of these, 113 cases had data to estimate the date

of seroconversion, defined by a negative HIV test followed by a positive HIV test within three years. Table 1 summarizes the characteristics of the eligible cases used for fitting the initial and second regression models. The median of first CD4 counts was 489 cells/mm<sup>3</sup> (interquartile range [IQR]: 372-620 cell/mm<sup>3</sup>), with 48% of cases having an initial CD4 count ≥ 500 cells/mm<sup>3</sup>.

For CD4 cell count declines without ART, Table 2 presents the intercept and slope estimates from the linear mixed-effects CD4 depletion model by age and gender. For males, the rate of decline in the square root of CD4 count (slope) ranged from -1.21 (95% CI: -1.24 to -1.18) in the youngest group (15-29 years) to -1.48 (95% CI: -1.51 to -1.44) in the oldest group (≥ 40 years). For females, the rate of decline ranged from -1.22 (95% CI: -1.25 to -1.19) in the youngest group to -1.46 (95% CI: -1.50 to -1.41) in the oldest group. The intercepts, representing the square root of the model-estimated CD4 cell count at the time of seroconversion, varied slightly, with the lowest intercept observed in the

30-39 age group for both males and females. Intercepts for females were consistently lower than those for males. The intercept for males in the 15-29 and ≥ 40 age groups were 24.42 (95% CI: 22.64 to 26.20) and 24.04 (95% CI: 21.28 to 26.80), respectively. For females, the intercepts were 23.80 (95% CI: 21.49 to 26.12) and 22.62 (95% CI: 20.36 to 24.87), respectively. Overall, the average intercept and slope were 23.64 (22.41 to 24.87) and -1.32 (-1.34 to -1.30) for males, and 22.70 (21.00 to 24.40) and -1.29 (-1.31 to -1.27) for females.

A monotonic decline in CD4 count over time since seroconversion was observed, with steeper declines in the earlier years post-infection for both males and females across all age groups (Figure 1). Among males, the CD4 count trajectories of the 30-39 and ≥ 40 age groups crossed after four years of infection, indicating greater CD4 depletion in later years among older males (≥ 40 years). The 15-29 year group consistently exhibited the highest CD4 cell count over time since seroconversion for both males and females.

To our knowledge, this study represents the first national-level exploration of HIV disease progression among heterosexually infected individuals in China. We estimated the date of HIV seroconversion using national surveillance data and applied a mixed-effects CD4 depletion model to estimate the time from seroconversion to reaching three CD4 count thresholds.

Compared to Lodi *et al.* (9), our estimated times from seroconversion to reaching CD4 thresholds of < 500, < 350, and < 200 cells/mm<sup>3</sup> were shorter by approximately 1, 4, and 8 years, respectively. Although the reasons for these differences are unclear, they may be attributable to variations in race/ethnicity, HIV subtype, baseline disease condition, and non-ART treatment (11,15).

The linear mixed-effects model in this study effectively handles random effects between multilevel variables and is widely used in longitudinal data analyses involving repeated CD4 measurements (19,21). Our model demonstrated a negative relationship between CD4 count and time since infection, with a greater rate of decline among older adults. These findings align with results from studies conducted in the United States (9), Brazil (10), and Europe (15).

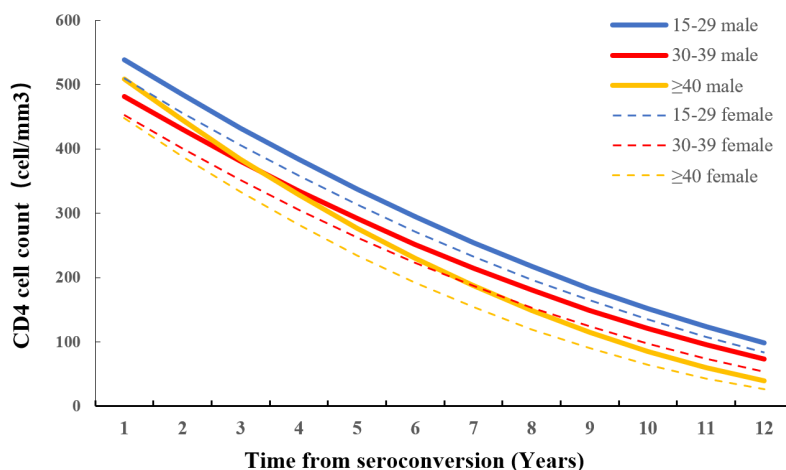
**Table 1. Characteristics of 59 085 HIV/AIDS cases included in this study**

Variable	n	(%)
Gender		
Male	34 337	58.11
Female	24 748	41.89
Age group*		
15-29	19 984	33.83
30-39	16 499	27.93
≥ 40	22 594	38.25
Education		
Primary/illiterate	19 245	32.57
Junior high	25 560	43.26
Senior high and above	14 280	24.17
Ethnic group		
Han	43 506	73.63
Others	15 579	26.37
First CD4 cell count (cells/mm <sup>3</sup> )		
< 200	4 261	7.21
200-349	7 749	13.12
350-499	18 778	31.78
≥ 500	28 297	47.89
Total	59 085	100.00

Note: \*There were 8 cases with missing information on age.

**Table 2. Intercept and slope estimates from liner mixed-effects CD4 depletion model, by age and gender**

Gender	Age group	Cases for intercept estimates				p value	Cases for slope estimates			
		Cases	Intercept	95% CI	p value		Cases	Slope	95% CI	p value
Male	15-29y	22	24.42	22.64 - 26.20	< 0.001	9656	-1.21	-1.24 - -1.18	< 0.001	
	30-39y	28	23.17	21.25 - 25.08	< 0.001	10005	-1.27	-1.30 - -1.24	< 0.001	
	≥ 40y	26	24.04	21.28 - 26.80	< 0.001	14675	-1.48	-1.51 - -1.44	< 0.001	
	subtotal	76	23.64	22.41 - 24.87	< 0.001	34336	-1.3	-1.34 - -1.30	< 0.001	
Female	15-29y	10	23.80	21.49 - 26.12	< 0.001	10328	-1.22	-1.25 - -1.19	< 0.001	
	30-39y	9	22.55	17.73 - 27.37	< 0.001	6494	-1.27	-1.31 - -1.23	< 0.001	
	≥ 40y	18	22.62	20.36 - 24.87	< 0.001	7919	-1.46	-1.50 - -1.41	< 0.001	
	subtotal	37	22.70	21.00 - 24.40	< 0.001	24741	-1.29	-1.31 - -1.27	< 0.001	



**Figure 1. CD4 cell count decline over time since HIV seroconversion by age and gender based on the linear mixed-effects CD4 depletion model.**

**Table 3. Median estimated time from seroconversion to CD4 cell count < 500, < 350, < 200 cell/mm<sup>3</sup> by age**

Variable	CD4 < 500		CD4 < 350		CD4 < 200	
	Male	Female	Male	Female	Male	Female
15-29y						
Median (95% CI)	1.70 (0.23-3.25)	1.18 (0.00-3.16)	4.72 (3.17-6.35)	4.17 (2.23-4.23)	8.49 (6.85-10.22)	7.92 (5.88-10.07)
30-39y						
Median (95% CI)	0.64 (0.00-2.19)	0.15 (0.00-4.07)	3.51 (1.96-5.14)	3.02 (0.00-7.04)	7.11 (5.47-8.82)	6.62 (2.74-10.75)
≥ 40y						
Median (95% CI)	1.13 (0.00-3.08)	0.18 (0.00-1.78)	3.60 (1.70-5.62)	2.68 (1.10-4.37)	6.69 (4.73-8.79)	5.81 (4.15-7.61)
Total						
Median (95% CI)	0.97 (0.04-1.93)	0.26 (0.00-1.61)	3.74 (2.76-4.74)	3.09 (1.75-4.48)	7.20 (6.17-8.25)	6.48 (5.12-7.89)

Table 3 shows estimated time intervals from HIV seroconversion to reaching CD4 cell count thresholds of < 500, <350 and < 200 cells/mm<sup>3</sup> by age (Year) and gender. Notably, females tend to reach these thresholds sooner than males, while the youngest age group (15-29 years) reached thresholds the slowest, highlighting faster disease progression in females and slowest progression in the youngest age group. Specifically, males took 6-10 months longer to reach the CD4 thresholds compared to females of the same age. Median times from HIV infection to reaching CD4 thresholds of < 500, < 350, and < 200 cells/mm<sup>3</sup> were 0.97, 3.74, and 7.20 years for males, and 0.26, 3.09, and 6.48 years for females. These findings contrast with a previous study showing longer times for women to reaching CD4 cell counts of < 500, < 350, and < 200 cells/mm<sup>3</sup> than men, despite a similar pace of CD4 decline (11). CD4 stands as a pivotal biomarker for monitoring HIV disease progression, and researchers generally refer to median time after HIV seroconversion as an indicator of disease progression (22). Our results reveal shorter median times from seroconversion to the three CD4 cell count thresholds for women than for men. The disparity might potentially be attributed to varying initial CD4 levels between genders. Lodi and

colleagues proposed that men experience a steeper CD4 decline than women after seroconversion. However, our analysis found little difference in CD4 decline rate by gender, which was not influenced by regional or ethnic stratification. A Singapore cohort study emphasized a significant impact of the infecting subtype, especially subtype CRF01\_AE, on the rate of CD4 decline (14). Therefore, further exploration is needed to understand the relationship between HIV subtype and the rate of CD4 decline by gender.

Our analysis revealed that the rate of CD4 decline was faster among older individuals and that females experienced faster disease progression than males. Among heterosexually infected individuals, females had faster disease progression, with an estimated time from seroconversion to reaching CD4 thresholds six to ten months sooner than males. The initial CD4 cell counts at HIV seroconversion were highest in the 15-29 age group, with the rate of CD4 count decline increasing with age.

Since China implemented the "treat-all" policy in 2016, studying the natural history and disease progression of PLHIV has become more challenging. Using the national surveillance database and a linear mixed-effects model based on CD4 depletion modelling



methods, we were able to explore HIV disease progression at the national level. The estimated rate of CD4 decline can inform back-calculation of the distribution of years since infection, aiding estimation of new infections in China.

Our study has several limitations. First, the estimation for seroconversion date as the midpoint between the last negative HIV test date and first positive HIV test date within a three-year interval may compromise accuracy and precision. Additionally, the small number of cases with a negative HIV test within three years prior to a positive test could impact the precision and generalizability of the intercept estimates. However, the slope estimates, based on all 59 085 eligible patients, mitigate these concerns. The lack of information on HIV subtype and other disease prognostic factors also limits our ability to address patient heterogeneity.

In conclusion, the rate of CD4 decline was faster among older ages and females in China, with progression to CD4 thresholds occurring faster in women and older age groups ( $\geq 40$  years) than men and younger age group (15-29 years). Further studies should utilize the modeled CD4 decline rate to estimate new infections who acquired HIV through heterosexual contact, which can help decision-makers evaluate the effectiveness of HIV prevention and control measures in China.

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**Conflict of Interest:** The authors have no conflicts of interest to disclose.

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