

## Vital Surveillances

# Five-Year Immune Recovery After ART Initiation Among PLWH Aged $\geq 15$ Years with Baseline Immunosuppression — China, 2013–2024

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## ABSTRACT

**Introduction:** Although antiretroviral therapy (ART) suppresses human immunodeficiency virus (HIV) replication in most people living with HIV (PLWH), 10%–40% show inadequate CD4 reconstitution despite sustained virologic suppression, increasing risks of AIDS- and non-AIDS-related events. Prior studies have suggested that immunological nonresponse (INR) is particularly common among individuals starting ART with immunosuppression. In China, real-world evidence for long-term immune recovery in immunosuppressed PLWH remains limited.

**Methods:** Immunosuppression was defined as a baseline CD4 < 350 cells/ $\mu$ L at ART initiation. At year 5, INR was defined as CD4 < 350 cells/ $\mu$ L and favorable immune recovery as CD4  $\geq$  500 cells/ $\mu$ L. From China's National ART Cohort, we included PLWH (aged  $\geq 15$  years; baseline CD4 < 350 cells/ $\mu$ L) initiating ART during 2013–2019 who achieved year-5 virologic suppression ( $\leq 50$  copies/mL). We described 5-year CD4 changes and examined factors associated with year-5 immune outcomes.

**Results:** Among 315,109 participants, the median CD4 count increased from 199 cells/ $\mu$ L at baseline to 424 cells/ $\mu$ L over 5 years of ART. At year 5, 111,899 (35.5%) had CD4  $\geq$  500 cells/ $\mu$ L (favorable immune recovery). In contrast, 109,344 (34.7%) patients had a CD4 < 350 cells/ $\mu$ L and were classified as having INR. Lower baseline CD4 counts, older age, male sex, heterosexual or injection drug transmission, HBsAg positivity, anti-HCV positivity, and delayed ART initiation were associated with higher odds of INR. Compared to continuous non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy, continuous protease inhibitor (PI)- and integrase strand transfer inhibitor (INSTI)-based therapies, and switching from NNRTI- to INSTI-based regimens showed higher odds of favorable immune recovery.

**Conclusions:** Among PLWH who initiated ART with immunosuppression and achieved virologic suppression at 5 years, most experienced immune recovery; however, approximately one-third remained INR. Early diagnosis, timely ART initiation, and targeted long-term immunological monitoring are required for populations at increased risk of suboptimal immune recovery.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) set the "95–95–95" targets, underscoring antiretroviral therapy (ART) as a cornerstone of human immunodeficiency virus (HIV) control. However, immune recovery after ART remains heterogeneous, and even among people living with HIV (PLWH) with sustained virologic suppression, an estimated 10%–40% do not achieve favorable CD4 recovery and consequently face elevated risks of AIDS- and non-AIDS-related events (1–2). In China, free ART has been available since 2004 under the "Four Frees and One Care" policy, and ART coverage and virologic suppression rates have exceeded 90% in recent years (3). Nevertheless, a substantial proportion of PLWH continue to initiate ART late, and real-world evidence of long-term immune recovery and its determinants in this population remains limited. Therefore, immune recovery at 5 years after ART initiation was assessed, and factors associated with immunological nonresponse (INR) (CD4 < 350 cells/ $\mu$ L) and favorable immune recovery (CD4  $\geq$  500 cells/ $\mu$ L) were examined among PLWH in China with immunosuppression at ART initiation (2).

## METHODS

### Data Sources

Study data were derived from the National ART

Cohort in China and extracted from the National Free Antiretroviral Treatment Information System, which is maintained by the China Centers for Disease Control and Prevention and quality-controlled under the National Quality Assurance Program. This system has been described in detail in previously published studies (4). Because China's 2012 treatment guidelines expanded free ART eligibility to patients with CD4 <350 cells/ $\mu$ L, this study included persons aged  $\geq 15$  years who initiated ART during 2013–2019 and were followed through June 30, 2025, ensuring that all participants had the opportunity to complete 5 years of follow-up (60 months after ART initiation;  $\pm 6$  months). PLWH initiating ART with immunosuppression (baseline CD4 <350 cells/ $\mu$ L) (5) were included if they had a year-5 CD4 measurement and two consecutive viral load measurements  $\leq 50$  copies/mL (1).

### Definitions

Initiation of ART with immunosuppression was defined as baseline CD4 <350 cells/ $\mu$ L (5). Baseline CD4 count was defined as the CD4 measurement obtained within 30 days before ART initiation and was categorized as <100, 100–199, and 200–349 cells/ $\mu$ L. Follow-up CD4 counts at years 1–5 were ascertained within predefined windows (12 $\times$ N months after ART initiation,  $\pm 6$  months), selecting the measurement closest to 12 $\times$ N months. Virologic suppression was defined as two consecutive viral load measurements  $\leq 50$  copies/mL before the year-5 CD4 date (1). Among PLWH with virologic suppression at year 5, immunological non-response (INR) was defined as a CD4 <350 cells/ $\mu$ L at year 5 (1). Favorable immune recovery was defined as a CD4  $\geq 500$  cells/ $\mu$ L at year 5 (2).

### Study Design

This study was a retrospective cohort study. Baseline variables included sex, age at ART initiation, marital status, route of HIV transmission, time from HIV diagnosis to ART initiation, baseline CD4 count, hepatitis B surface antigen (HBsAg) status, anti-HCV serostatus, and ART regimen. To describe immune recovery, baseline characteristics were summarized as counts (percentages), and baseline and year-5 CD4 counts were reported as medians with interquartile ranges (IQR). CD4 at year 5 was categorized as <200, 200–349, 350–499, and  $\geq 500$  cells/ $\mu$ L, and frequencies (percentages) were calculated overall and

across baseline subgroups. The distribution of CD4 categories at baseline and each annual follow-up throughout year 5 was summarized using 100% stacked bar charts. Median CD4 trajectories from years 1 to 5 were also plotted, stratified by baseline CD4 category (<100, 100–199, 200–349 cells/ $\mu$ L) and age group (15–30, 31–45, 46–60,  $\geq 61$  years). Finally, among PLWH with virologic suppression at year 5, determinants of INR (CD4 <350 cells/ $\mu$ L) and favorable immune recovery (CD4  $\geq 500$  cells/ $\mu$ L) were evaluated.

### Statistical Analysis

Group differences in the year-5 CD4 categories were assessed using the chi-square test. Factors associated with INR and favorable immune recovery at year 5 were examined using univariable logistic regression, and variables with  $P < 0.05$  and clinical relevance were included in multivariable logistic regression models. The results are presented as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Analyses were conducted in R (version 4.4.3; R Foundation for Statistical Computing, Vienna, Austria), and two-sided  $P < 0.05$  indicated statistical significance.

## RESULTS

### Cohort Characteristics and Year-5 CD4 Distribution

Among the 460,161 participants with a baseline CD4 <350 cells/ $\mu$ L, 71,048 (15%) died before the year-5 assessment window and 22,553 (5%) had no CD4 measurement within the year-5 window. Among those with an available year-5 CD4 result, 315,109 (86%) achieved virological suppression and were included in the final analysis. A total of 315,109 participants were included, of whom 241,028 (76.5%) were male. Heterosexual contact was the most frequently reported route of HIV transmission (194,373; 61.7%). At baseline, CD4 cell counts of <100, 100–199, and 200–349 cells/ $\mu$ L were observed in 79,436 (25.2%), 79,028 (25.1%), and 156,645 (49.7%) participants, respectively. At year 5 after ART initiation, the median CD4 cell count was 424 cells/ $\mu$ L (IQR: 300, 570) and CD4 categories of <200, 200–349, 350–499, and  $\geq 500$  cells/ $\mu$ L accounted for 28,107 (8.9%), 81,237 (25.8%), 93,866 (29.8%), and 111,899 (35.5%) participants, respectively (Table 1).

Across follow-up, the proportion of PLWH with CD4 <350 cells/ $\mu$ L decreased from 100% at baseline

TABLE 1. Year-5 CD4 cell count distribution by selected characteristics among PLWH initiating ART with baseline CD4<350 cells/ $\mu$ L and virologic suppression at year 5 in China, 2013–2024 (N=315,109).

| Variable                                         | Total n (%)       | CD4 at baseline, cells/ $\mu$ L<br>median (IQR) | CD4 at year 5, cells/ $\mu$ L<br>median (IQR) | CD4 count at year 5 (cells/ $\mu$ L) |                  |                  |                  | P     |
|--------------------------------------------------|-------------------|-------------------------------------------------|-----------------------------------------------|--------------------------------------|------------------|------------------|------------------|-------|
|                                                  |                   |                                                 |                                               | <200                                 | 200–349          | 350–499          | $\geq$ 500       |       |
|                                                  |                   |                                                 |                                               | n (%)                                | n (%)            | n (%)            | n (%)            |       |
| Gender                                           |                   |                                                 |                                               |                                      |                  |                  |                  | <0.01 |
| Male                                             | 241,028<br>(76.5) | 196<br>(92, 273)                                | 418<br>(294, 564)                             | 23,070<br>(9.6)                      | 63,478<br>(26.3) | 71,124<br>(29.5) | 83,356<br>(34.6) |       |
| Female                                           | 74,081<br>(23.5)  | 205<br>(116, 275)                               | 442<br>(321, 587)                             | 5,037<br>(6.8)                       | 17,759<br>(24.0) | 22,742<br>(30.7) | 28,543<br>(38.5) |       |
| Age at ART initiation (years)                    |                   |                                                 |                                               |                                      |                  |                  |                  | <0.01 |
| 15–30                                            | 83,222<br>(26.4)  | 230<br>(137, 292)                               | 489<br>(368, 632)                             | 3,093<br>(3.7)                       | 14,750<br>(17.7) | 25,900<br>(31.1) | 39,479<br>(47.4) |       |
| 31–45                                            | 111,090<br>(35.3) | 191<br>(84, 270)                                | 432<br>(311, 577)                             | 8,547<br>(7.7)                       | 27,800<br>(25.0) | 33,790<br>(30.4) | 40,953<br>(36.9) |       |
| 46–60                                            | 82,578<br>(26.2)  | 180<br>(84, 259)                                | 386<br>(269, 528)                             | 9,857<br>(11.9)                      | 25,031<br>(30.3) | 23,821<br>(28.9) | 23,869<br>(28.9) |       |
| $\geq$ 61                                        | 38,219<br>(12.1)  | 185<br>(108, 256)                               | 335<br>(234, 464)                             | 6,610<br>(17.3)                      | 13,656<br>(35.7) | 10,355<br>(27.1) | 7,598<br>(19.9)  |       |
| Marital status                                   |                   |                                                 |                                               |                                      |                  |                  |                  | <0.01 |
| Unmarried                                        | 94,463<br>(30.0)  | 217<br>(111, 286)                               | 471<br>(348, 615)                             | 4,952<br>(5.2)                       | 18,919<br>(20.0) | 29,071<br>(30.8) | 41,521<br>(44.0) |       |
| Married or with partner                          | 167,031<br>(53.0) | 191<br>(95, 267)                                | 404<br>(284, 548)                             | 17,134<br>(10.3)                     | 47,032<br>(28.2) | 49,316<br>(29.5) | 53,549<br>(32.1) |       |
| Divorced or widowed                              | 53,615<br>(17.0)  | 189<br>(94, 267)                                | 400<br>(278, 545)                             | 6,021<br>(11.2)                      | 15,286<br>(28.5) | 15,479<br>(28.9) | 16,829<br>(31.4) |       |
| Route of transmission                            |                   |                                                 |                                               |                                      |                  |                  |                  | <0.01 |
| Heterosexual transmission                        | 194,373<br>(61.7) | 189<br>(92, 267)                                | 405<br>(284, 550)                             | 20,508<br>(10.6)                     | 54,276<br>(27.9) | 56,839<br>(29.2) | 62,750<br>(32.3) |       |
| MSM transmission                                 | 90,701<br>(28.8)  | 219<br>(120, 286)                               | 469<br>(348, 609)                             | 4,403<br>(4.9)                       | 18,449<br>(20.3) | 28,430<br>(31.3) | 39,419<br>(43.5) |       |
| Injection drug use                               | 9,961<br>(3.2)    | 207<br>(122, 276)                               | 387<br>(262, 533)                             | 1,313<br>(13.2)                      | 2,922<br>(29.3)  | 2,744<br>(27.6)  | 2,982<br>(29.9)  |       |
| Other                                            | 20,074<br>(6.4)   | 179<br>(74, 265)                                | 414<br>(290, 559)                             | 1,883<br>(9.4)                       | 5,590<br>(27.9)  | 5,853<br>(29.2)  | 6,748<br>(33.6)  |       |
| Time from HIV diagnosis to ART initiation (days) |                   |                                                 |                                               |                                      |                  |                  |                  | <0.01 |
| 0–6                                              | 39,490<br>(12.5)  | 179<br>(80, 260)                                | 410<br>(289, 558)                             | 3,863<br>(9.8)                       | 10,824<br>(27.4) | 11,551<br>(29.3) | 13,252<br>(33.6) |       |
| 7–30                                             | 130,583<br>(41.4) | 186<br>(84, 264)                                | 420<br>(297, 564)                             | 11,816<br>(9.1)                      | 34,514<br>(26.4) | 39,033<br>(29.9) | 45,220<br>(34.6) |       |
| 31–360                                           | 98,503<br>(31.3)  | 211<br>(114, 280)                               | 424<br>(302, 567)                             | 8,748<br>(8.9)                       | 25,159<br>(25.5) | 29,705<br>(30.2) | 34,891<br>(35.4) |       |
| >360                                             | 46,533<br>(14.8)  | 221<br>(126, 288)                               | 447<br>(317, 599)                             | 3,680<br>(7.9)                       | 10,740<br>(23.1) | 13,577<br>(29.2) | 18,536<br>(39.8) |       |
| Baseline CD4 count (cells/ $\mu$ L)              |                   |                                                 |                                               |                                      |                  |                  |                  | <0.01 |
| 0–99                                             | 79,436<br>(25.2)  | 38<br>(17, 67)                                  | 310<br>(217, 431)                             | 16,257<br>(20.5)                     | 31,006<br>(39.0) | 19,455<br>(24.5) | 12,718<br>(16.0) |       |
| 100–199                                          | 79,028<br>(25.1)  | 155<br>(129, 178)                               | 382<br>(282, 504)                             | 7,135<br>(9.0)                       | 25,939<br>(32.8) | 25,716<br>(32.5) | 20,238<br>(25.6) |       |
| 200–349                                          | 156,645<br>(49.7) | 274<br>(237, 310)                               | 502<br>(385, 643)                             | 4,715<br>(3.0)                       | 24,292<br>(15.5) | 48,695<br>(31.1) | 78,943<br>(50.4) |       |
| HBsAg                                            |                   |                                                 |                                               |                                      |                  |                  |                  | <0.01 |
| Positive                                         | 22,746<br>(7.2)   | 187<br>(89, 265)                                | 403<br>(285, 545)                             | 2,290<br>(10.1)                      | 6,530<br>(28.7)  | 6,750<br>(29.7)  | 7,176<br>(31.5)  |       |
| Negative                                         | 220,808<br>(70.1) | 201<br>(102, 275)                               | 429<br>(305, 575)                             | 18,893<br>(8.6)                      | 55,628<br>(25.2) | 65,978<br>(29.9) | 80,309<br>(36.4) |       |
| Missing/Unknown                                  | 71,555<br>(22.7)  | 193<br>(89, 272)                                | 416<br>(293, 562)                             | 6,924<br>(9.7)                       | 19,079<br>(26.7) | 21,138<br>(29.5) | 24,414<br>(34.1) |       |

Continued

| Variable                     | Total <i>n</i><br>(%) | CD4 at baseline,<br>cells/ $\mu$ L | CD4 at year 5,<br>cells/ $\mu$ L | CD4 count at year 5 (cells/ $\mu$ L) |                  |                  |                   | <i>P</i> |
|------------------------------|-----------------------|------------------------------------|----------------------------------|--------------------------------------|------------------|------------------|-------------------|----------|
|                              |                       |                                    |                                  | <200                                 | 200–349          | 350–499          | $\geq 500$        |          |
|                              |                       | median (IQR)                       | median (IQR)                     | <i>n</i> (%)                         | <i>n</i> (%)     | <i>n</i> (%)     | <i>n</i> (%)      |          |
| Anti-HCV                     |                       |                                    |                                  |                                      |                  |                  |                   | <0.01    |
| Positive                     | 13,400<br>(4.3)       | 198<br>(111, 272)                  | 400<br>(275, 548)                | 1,560<br>(11.6)                      | 3,775<br>(28.2)  | 3,786<br>(28.3)  | 4,279<br>(31.9)   |          |
| Negative                     | 226,906<br>(72.0)     | 200<br>(101, 274)                  | 429<br>(305, 574)                | 19,209<br>(8.5)                      | 57,405<br>(25.3) | 67,961<br>(30.0) | 82,331<br>(36.3)  |          |
| Missing/Unknown              | 74,803<br>(23.7)      | 194<br>(89, 272)                   | 415<br>(292, 560)                | 7,338<br>(9.8)                       | 20,057<br>(26.8) | 22,119<br>(29.6) | 25,289<br>(33.8)  |          |
| ART Regimen                  |                       |                                    |                                  |                                      |                  |                  |                   | <0.01    |
| Continuous NNRTI-based       | 296,787<br>(94.2)     | 201<br>(103, 275)                  | 423<br>(300, 568)                | 26,457<br>(8.9)                      | 76,835<br>(25.9) | 88,676<br>(29.9) | 104,819<br>(35.3) |          |
| Continuous PI-based          | 12,546<br>(4.0)       | 163<br>(54, 258)                   | 449<br>(313, 606)                | 1,091<br>(8.7)                       | 2,866<br>(22.8)  | 3,504<br>(27.9)  | 5,085<br>(40.5)   |          |
| Continuous INSTI-based       | 3,435<br>(1.1)        | 93<br>(24, 215)                    | 425<br>(297, 578)                | 293<br>(8.5)                         | 906<br>(26.4)    | 1,008<br>(29.3)  | 1,228<br>(35.7)   |          |
| Switched from NNRTI to INSTI | 1,090<br>(0.3)        | 53<br>(18, 159)                    | 382<br>(272, 519)                | 134<br>(12.3)                        | 319<br>(29.3)    | 330<br>(30.3)    | 307<br>(28.2)     |          |
| Switched from NNRTI to PI    | 1,251<br>(0.4)        | 192<br>(83, 271)                   | 422<br>(290, 579)                | 132<br>(10.6)                        | 311<br>(24.9)    | 348<br>(27.8)    | 460<br>(36.8)     |          |
| Total                        | 315,109<br>(100)      | 199<br>(99, 273)                   | 424<br>(300, 570)                | 28,107<br>(8.9)                      | 81,237<br>(25.8) | 93,866<br>(29.8) | 111,899<br>(35.5) |          |

Note: *P* values were obtained from chi-square tests comparing the distribution of year-5 CD4 categories across the subgroups.

Abbreviation: HIV=human immunodeficiency virus; PLWH=people living with HIV; ART=antiretroviral therapy; IQR=interquartile range; HBsAg=hepatitis B surface antigen; anti-HCV=antibody to hepatitis C virus; MSM=men who have sex with men; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; INSTI=integrase strand transfer inhibitor.

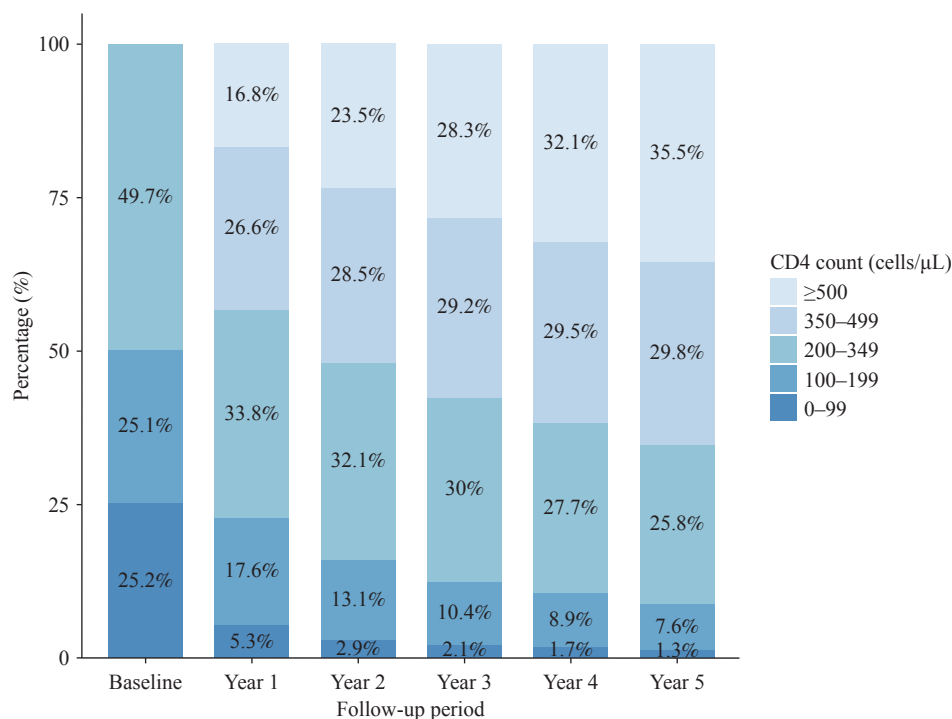


FIGURE 1. Distribution of CD4 cell count categories from baseline to year 5 after ART initiation among PLWH with baseline CD4 <350 cells/ $\mu$ L and virologic suppression at year 5 in China, 2013–2024 (*N*=315,109).

Note: Bars show 100% stacked percentages at baseline and 1–5 years after ART initiation. Virologic suppression was defined as two consecutive viral load measurements  $\leq 50$  copies/mL before the year-5 CD4 date.

Abbreviation: HIV=human immunodeficiency virus; PLWH=people living with HIV; ART=antiretroviral therapy.

to 56.5% at year 1, 48.0% at year 2, 42.5% at year 3, 38.4% at year 4, and 34.7% at year 5 (Figure 1). At year 5, 35.5% had CD4 $\geq$ 500 cells/ $\mu$ L (favorable immune recovery) (Figure 1). In the line plots of median CD4 count, the largest year-to-year increase occurred between baseline and year 1 across all groups (Figure 2). For example, the median CD4 count increased by 142 cells/ $\mu$ L from baseline to year 1 in the baseline CD4 200–349 cells/ $\mu$ L group and by 144 cells/ $\mu$ L in the 15–30 years old age group (Figure 2).

### Factors Associated with Immune Recovery at Year 5

In multivariable analyses, compared with baseline CD4 200–349 cells/ $\mu$ L, baseline CD4 100–199 cells/ $\mu$ L and <100 cells/ $\mu$ L were associated with higher odds of INR (aOR=2.99 and 6.64, respectively). They were also associated with lower odds of achieving CD4  $\geq$ 500 cells/ $\mu$ L (aOR=0.36 and 0.19, respectively) (Table 2). Age at ART initiation showed a dose–response pattern. Compared with those aged 15–30 years, older age groups had higher odds of INR (31–45 years: aOR=1.33; 46–60 years: aOR=2.04;  $\geq$ 61 years: aOR=3.49). In parallel, the odds of achieving CD4  $\geq$ 500 cells/ $\mu$ L decreased with age (aOR=0.83, 0.58, and 0.33, respectively). Compared with females,

males had higher odds of INR (aOR=1.49; 95% CI: 1.46, 1.52) (Table 2).

Compared with continuous non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy, continuous protease inhibitor (PI)-based therapy was associated with higher odds of achieving favorable immune recovery (CD4 $\geq$ 500 cells/ $\mu$ L) (aOR=1.54; 95% CI: 1.48, 1.60). A similar association was observed for continuous integrase strand transfer inhibitor (INSTI)-based therapy (aOR=1.42; 95% CI: 1.32, 1.54). Switching from an NNRTI-based regimen to an INSTI-based regimen was also associated with higher odds of CD4 $\geq$ 500 cells/ $\mu$ L (aOR=1.23; 95% CI: 1.07, 1.42) (Table 2). In addition, injection drug use, HBsAg/anti-HCV positivity, and delayed ART initiation were independently associated with higher INR odds (Table 2).

### DISCUSSION

The objectives of ART include both sustained virological suppression and immune reconstitution, with the overarching aim of improving long-term survival and quality of life (1). Prior studies have shown that INR signifies persistent immune dysfunction and is associated with an increased risk of

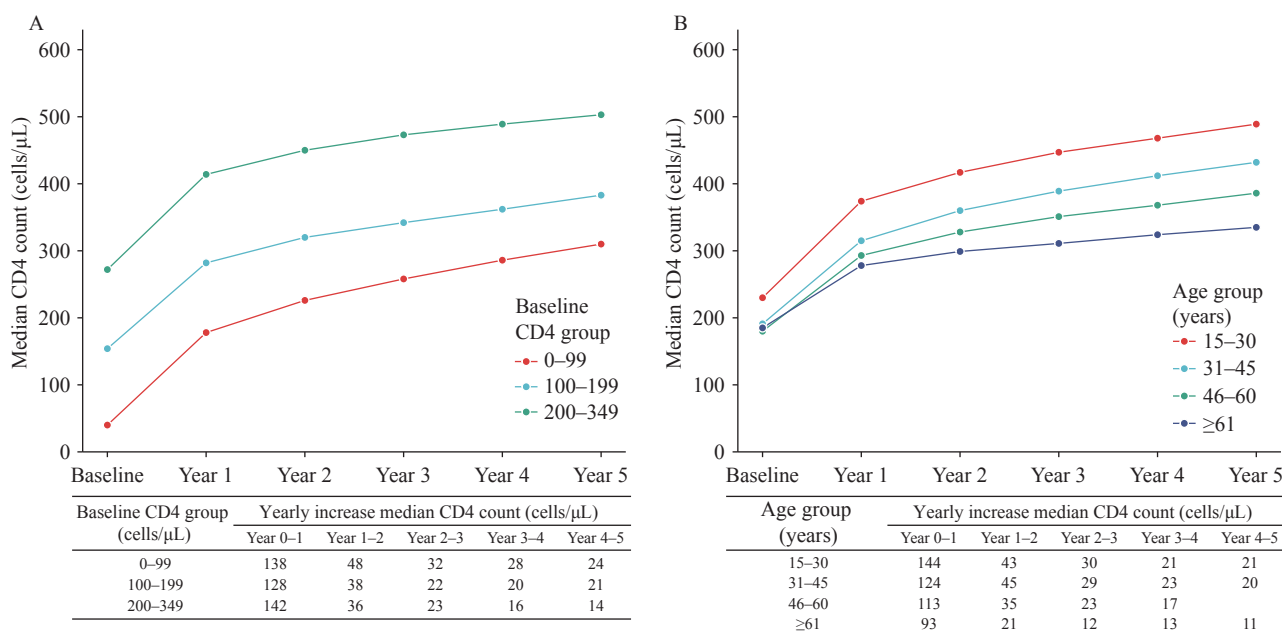


FIGURE 2. Median CD4 cell count trajectories from baseline to year 5 after ART initiation, stratified by (A) baseline CD4 category and (B) age at ART initiation, among PLWH with baseline CD4 <350 cells/ $\mu$ L and virologic suppression at year 5 — China, 2013–2024 (N=315,109).

Note: Panel A groups: 0–99, 100–199, and 200–349 cells/ $\mu$ L. Panel B groups: 15–30, 31–45, 46–60, and  $\geq$ 61 years. Abbreviation: HIV=human immunodeficiency virus; PLWH=people living with HIV; ART=antiretroviral therapy.

TABLE 2. Multivariable factors associated with immunological non-response (INR; CD4<350 cells/ $\mu$ L) and favorable immune recovery (CD4 $\geq$ 500 cells/ $\mu$ L) at year 5 among PLWH initiating ART with baseline CD4<350 cells/ $\mu$ L and virologic suppression at year 5 in China, 2013–2024 (N=315,109).

| Variable                                         | CD4 $\geq$ 500 (cells/ $\mu$ L) |       | CD4<350 (cells/ $\mu$ L) |       |
|--------------------------------------------------|---------------------------------|-------|--------------------------|-------|
|                                                  | Adjusted OR (95% CI)            | P     | Adjusted OR (95% CI)     | P     |
| Gender                                           |                                 |       |                          |       |
| Female                                           | 1.00 (Reference)                |       | 1.00 (Reference)         |       |
| Male                                             | 0.73 (0.72, 0.75)               | <0.01 | 1.49 (1.46, 1.52)        | <0.01 |
| Age at ART initiation (years)                    |                                 |       |                          |       |
| 15–30                                            | 1.00 (Reference)                |       | 1.00 (Reference)         |       |
| 31–45                                            | 0.83 (0.81, 0.85)               | <0.01 | 1.33 (1.30, 1.36)        | <0.01 |
| 46–60                                            | 0.58 (0.57, 0.60)               | <0.01 | 2.04 (1.98, 2.09)        | <0.01 |
| $\geq$ 61                                        | 0.33 (0.32, 0.34)               | <0.01 | 3.49 (3.37, 3.61)        | <0.01 |
| Marital Status                                   |                                 |       |                          |       |
| Unmarried                                        | 1.00 (Reference)                |       | 1.00 (Reference)         |       |
| Married or with partner                          | 0.89 (0.87, 0.91)               | <0.01 | 1.13 (1.10, 1.16)        | <0.01 |
| Divorced or widowed                              | 0.91 (0.89, 0.94)               | <0.01 | 1.14 (1.11, 1.17)        | <0.01 |
| Route of Transmission                            |                                 |       |                          |       |
| MSM transmission                                 | 1.00 (Reference)                |       | 1.00 (Reference)         |       |
| Injection drug use                               | 0.59 (0.56, 0.63)               | <0.01 | 2.07 (1.96, 2.19)        | <0.01 |
| Heterosexual transmission                        | 0.81 (0.79, 0.83)               | <0.01 | 1.38 (1.35, 1.41)        | <0.01 |
| Other                                            | 0.90 (0.87, 0.93)               | <0.01 | 1.25 (1.21, 1.30)        | <0.01 |
| Time from HIV diagnosis to ART initiation (days) |                                 |       |                          |       |
| 0–6                                              | 1.00 (Reference)                |       | 1.00 (Reference)         |       |
| 7–30                                             | 0.98 (0.95, 1.00)               | 0.07  | 1.00 (0.97, 1.02)        | 0.77  |
| 31–360                                           | 0.87 (0.84, 0.89)               | <0.01 | 1.14 (1.11, 1.17)        | <0.01 |
| >360                                             | 0.98 (0.95, 1.01)               | 0.17  | 1.07 (1.04, 1.10)        | <0.01 |
| Baseline CD4 cell count (cells/ $\mu$ L)         |                                 |       |                          |       |
| 200–349                                          | 1.00 (Reference)                |       | 1.00 (Reference)         |       |
| 0–99                                             | 0.19 (0.18, 0.19)               | <0.01 | 6.64 (6.50, 6.77)        | <0.01 |
| 100–199                                          | 0.36 (0.35, 0.36)               | <0.01 | 2.99 (2.93, 3.05)        | <0.01 |
| HBsAg                                            |                                 |       |                          |       |
| Negative                                         | 1.00 (Reference)                |       | 1.00 (Reference)         |       |
| Positive                                         | 0.85 (0.83, 0.88)               | <0.01 | 1.18 (1.14, 1.21)        | <0.01 |
| Missing/unknown                                  | 1.03 (1.00, 1.07)               | 0.04  | 0.97 (0.94, 0.99)        | <0.01 |
| Anti-HCV                                         |                                 |       |                          |       |
| Negative                                         | 1.00 (Reference)                |       | 1.00 (Reference)         |       |
| Positive                                         | 0.91 (0.87, 0.95)               | <0.01 | 1.14 (1.09, 1.20)        | <0.01 |
| Missing/unknown                                  | 0.93 (0.91, 0.96)               | <0.01 | 1.08 (1.05, 1.12)        | <0.01 |
| ART Regimen                                      |                                 |       |                          |       |
| Continuous NNRTI-based                           | 1.00 (Reference)                |       | 1.00 (Reference)         |       |
| Continuous PI-based                              | 1.54 (1.48, 1.60)               | <0.01 | 0.66 (0.63, 0.69)        | <0.01 |
| Continuous INSTI-based                           | 1.42 (1.32, 1.54)               | <0.01 | 0.70 (0.65, 0.76)        | <0.01 |
| Switch from NNRTI to INSTI                       | 1.23 (1.07, 1.42)               | <0.01 | 0.76 (0.67, 0.87)        | <0.01 |
| Switch from NNRTI to PI                          | 1.05 (0.93, 1.20)               | 0.41  | 1.02 (0.90, 1.16)        | 0.76  |

Abbreviation: HIV=human immunodeficiency virus; aOR=adjusted odds ratio; CI=confidence interval; INR=immunological nonresponse; PLWH=people living with HIV; ART=antiretroviral therapy; HBsAg=hepatitis B surface antigen; anti-HCV=antibody to hepatitis C virus; MSM=men who have sex with men; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; INSTI=integrase strand transfer inhibitor.

opportunistic infections, malignancies, and non-AIDS comorbidities, translating into two- to three-fold higher morbidity and mortality than those observed among immunological responders (2,6). By contrast, achieving favorable immune recovery ( $CD4 \geq 500$  cells/ $\mu$ L) is associated with morbidity and mortality approaching those of HIV-negative individuals (2). In this large real-world cohort study from China, with over 5 years of follow-up, median CD4 cell counts increased steadily, and the CD4 distribution shifted from lower to higher strata, consistent with previous findings (6). Nevertheless, heterogeneity in immune reconstitution persisted despite virological suppression. The analysis showed that 35.5% of participants achieved  $\geq 500$  cells/ $\mu$ L (favorable immune recovery) and 34.7% met criteria for immunological non-response (INR). These proportions were generally comparable to those reported in previous studies (32.9% and 36.1%, respectively) (7). In multivariable analysis, baseline CD4 count was the strongest predictor of achieving  $CD4 \geq 500$  cells/ $\mu$ L at year 5, consistent with reports from other settings. In a national laboratory-based analysis from South Africa, among PLWH who initiated ART with baseline  $CD4 < 50$  cells/ $\mu$ L, 71% of participants did not recover to  $CD4 \geq 200$  cells/ $\mu$ L by 12 months, and 39% of them did not reach this threshold during follow-up (8). Late ART initiation indicates advanced immune injury and is characterized by persistent immune activation and aberrant inflammation. Among people with a low baseline CD4 count, these abnormalities may not be fully resolved even after achieving virological suppression with ART. Individuals who initiate ART late often have a lower frequency of naïve  $CD4^+$  T cells and a higher proportion of effector memory T cells. This pattern suggests a reduced pool for expansion and replenishment, thereby limiting the magnitude of subsequent  $CD4^+$  T-cell recovery (2). Together, these findings support the current recommendations for the early diagnosis of HIV and prompt initiation of ART before profound CD4 depletion to maximize long-term immune recovery.

Older age at the time of ART initiation is associated not only with a reduced likelihood of achieving  $CD4 \geq 500$  cells/ $\mu$ L but also with an increased risk of remaining at  $CD4$  counts  $< 350$  cells/ $\mu$ L and is consistent with established evidence (9–10). This impaired CD4 recovery persists despite effective virological suppression and is largely attributed to age-related thymic involution, which limits the production of naïve T cells. This immunological deficit

may be further exacerbated by suboptimal treatment adherence in older PLWH (9). Supporting this, the Polish cohort data demonstrated significantly better immune reconstitution when ART was initiated before the age of 35 (10). These findings underscore the urgent need for targeted strategies for older populations, including the promotion of early HIV diagnosis, timely ART initiation, and enhanced support in areas such as nutrition and comorbidity management.

The findings showed that PI- or INSTI-based regimens, as well as switching from an NNRTI-based to an INSTI-based regimen, were associated with higher odds of achieving favorable immune recovery ( $CD4 \geq 500$  cells/ $\mu$ L). These associations are supported by previous studies. Protease inhibitors have been reported to suppress  $CD4^+$  T-cell apoptosis by targeting the mitochondrial permeability transition pore complex (PTPC), independent of their antiviral effects on HIV replication (11–12). Other studies have shown that INSTIs are associated with better immune recovery, particularly in patients with advanced disease (13–14). In the analysis, the association appeared slightly stronger for PI-based than for INSTI-based therapy (aOR=1.54; 95% CI: 1.48, 1.60 vs. aOR=1.42; 95% CI: 1.32, 1.54). Because the study required at least 5 years of continuous treatment, INSTI-based regimens were uncommon in this cohort, and INSTI exposure may have been too limited to fully capture the potential immunologic benefits.

This study has several limitations. First, this observational study was subject to residual confounding from unmeasured factors, such as ART adherence, socioeconomic status, and nutritional status. Second, requiring CD4 measurements at both baseline and year 5 excluded participants who died or were lost to follow-up before 5 years, likely leading to an overestimation of CD4 recovery due to healthy survivor bias. Third, INSTI-based regimens were uncommon in this cohort, limiting the statistical power to evaluate the association between regimen class and immune recovery.

In summary, among PLWH with baseline  $CD4 < 350$  cells/ $\mu$ L who achieved virologic suppression at year 5, most experienced substantial immune recovery; however, a considerable proportion remained in INR, highlighting marked heterogeneity in long-term immune reconstitution. These findings support the strengthening of early HIV diagnosis and timely ART initiation before a substantial CD4 decline. They also suggest the importance of risk-stratified long-term

immunologic monitoring and individualized management for patients at an increased risk of suboptimal immune recovery, including older individuals, those with low baseline CD4 counts, delayed ART initiation, HBsAg-positive or anti-HCV-positive status, and certain transmission groups. Additionally, integrated care and follow-up may improve long-term immune outcomes (15–16).

**Conflicts of interest:** No conflicts of interest.

**Ethical statement:** Approved by the Ethics Committee of the National Center for AIDS/STD Control and Prevention and the Chinese Center for Disease Control and Prevention (Approval No: KX230601731). The need for informed consent was waived because this study used routinely collected and deidentified data.

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